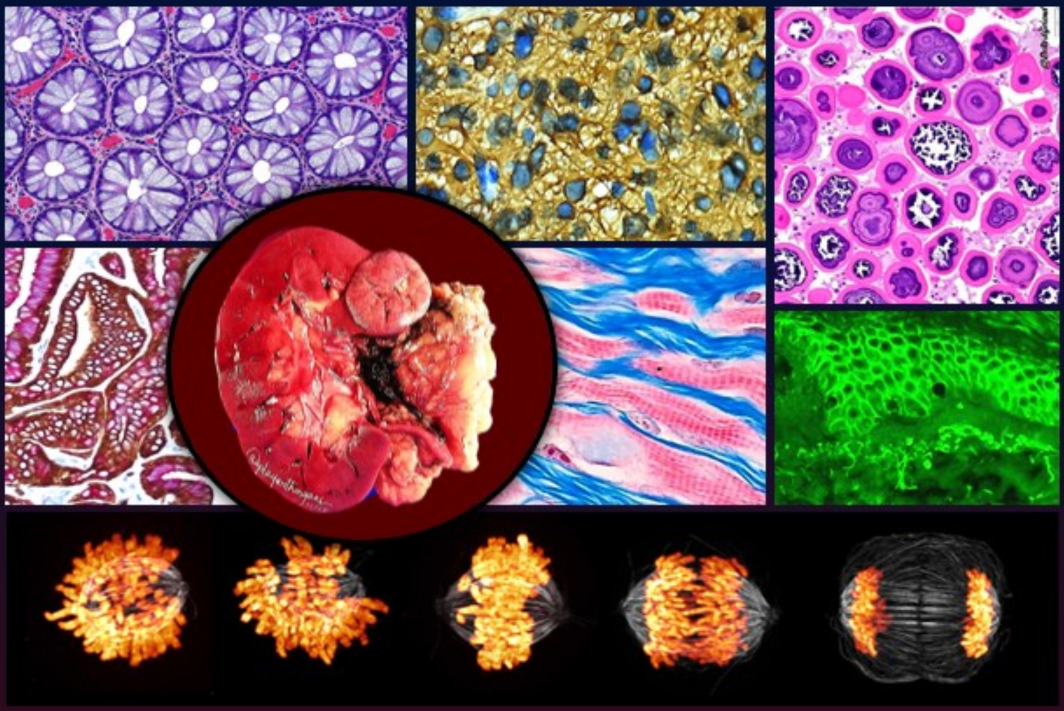
ACE THE BOARDS

SURGICAL PATHOLOGY REIMAGINED



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KURT'S NOTES
Ace My Path
PathPresenter

First Edition

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ACE MY PATH
Come Ace With Us!

KURT'S NOTES
PathPresenter

ACE THE BOARDS:
SURGICAL PATHOLOGY REIMAGINED

SALIENT FEATURES

- Kurt’s notes, extensively revised and updated, to reflect recent advances in Surgical Pathology.
- Access to over 1000 board-relevant whole slide images, along with annotated online “high yield sections” - virtual slide collection by Path Presenter.
- More than 4000 high-resolution gross, microscopic, immunohistochemistry, and ancillary images.
- 1500 online multiple-choice question modules (work in progress).
- Videos and audio explaining the material (work in progress).

HOW YOU CAN BENEFIT MOST FROM THE BOOK

- Start reading the material from the first year of the residency.
- QR codes for virtual slides:
  - ➢ Can be scanned in the print book using electronic devices, and it is compatible with Android and IOS.
  - ➢ Most of the current mobile devices allow scanning directly via the mobile camera.
  - ➢ The other option is to download any QR code scanner application from the play store/Appstore.
  - ➢ The words “Path Presenter, Link or PP Link” are clickable on the online eBook version of the book (works on android, PC and Mac – doesn’t work with some iPhones and iPads – contact us if it doesn’t work).
- High Yield Sections – Virtual Microscopy Hub:
  - ➢ This high-yield board-relevant hub can be purchased at acemypath.com.
  - ➢ High-yield sections are hosted via the website acemypath.pathpresenter.com.
  - ➢ These include system-wise, compiled, and annotated 1000 virtual slides in one place.
  - ➢ As a trial, these sections are currently available on pathpresenter.net free of cost for everyone.
- Multiple Choice Questions:
  - ➢ MCQs are a work in progress currently; we plan on publishing them within a month or two.
  - ➢ These can be purchased separately at acemypath.com and can be accessed online via acemypath.pathpresenter.com.
  - ➢ MCQs will be a mix of virtual slides-based, image-based, and text-based, per the board format.
  - ➢ Around 1500 MCQs will be available for AP, including cytopathology.
- Videos / Audios:
  - ➢ Videos and Audios are a work in progress currently; we plan on publishing them within a month or two.
  - ➢ These can be purchased separately at acemypath.com and can be accessed online via acemypath.pathpresenter.com.
  - ➢ In the videos and audio, our team will discuss entities and virtual slides in the book in a system-wise format.
  - ➢ Best for people on the go or away from their book or computer screen.

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KURT'S NOTES
PathPresenter

FOREWORD

“Surgical pathology is a complex, dynamic, and ever-evolving field of medicine. This book represents **a novel contribution** to the current pathology literature. The text is **thorough, yet concise, and up to date** with the most current concepts governing the practice of surgical pathology. The book has been designed to help pathology residents preparing for board examinations; however, it will also be a useful **quick reference for practicing pathologists**.

Increasingly, the students of today want information in digital form and not in printed form. Hence book authors must cater to the needs of the new generation. The editors of this book have therefore created **a “print” book with linkage to whole slide images by scanning a QR code**. One click takes the reader to annotations. Thus, this book simulates the traditional multihead scope teaching. The only difference is that this book has an **infinite headed scope**. This unique and first of its kind simulation of teaching will help readers solidify knowledge with real life examples of surgical pathology cases. Similarly, **audio content** is also available, giving users multiple formats to customize and optimize their learning experience.

The team of authors and editors have worked tirelessly to provide a **comprehensive, user-friendly, and innovative textbook** that will be very useful for pathology residents and fellows, as well as medical students, laboratory professionals, and seasoned pathologists already in practice. **I will recommend this to our residents, fellows, and faculty.** Congratulations to the Ace My Path team for creating a novel tool for pathology education.”

Vinay Kumar, MBBS, MD, FRCPath
Senior Editor/Author of Robbins Pathology textbooks
Lowell T Coggeshall Distinguished Service Professor of Pathology
Former Chairman of the Department of Pathology
Biologic Sciences Division and Pritzker School of Medicine
University of Chicago
Chicago, IL, USA

Dr Vinay Kumar is a passionate medical educator and has influenced medical education across the world for the past 35 years as the senior editor/author of **Robbins Pathology textbooks**. He is the senior editor of these books now in their 9th edition. Robbins Pathology is the most widely used medical text in the world with translations into **13 languages**. He is **the Alice Hogge and Arthur Baer Distinguished Service Professor and former Chairman** of the department of Pathology at the University of Chicago. He has made seminal contributions in the field of medical education and basic research. In 1974 **his laboratory identified Natural Killer (NK) cells** as a distinct population of lymphocytes with anti-tumor activities. Continuation of this work has led to discovery of NK cell receptors and the immunotherapeutic use of NK cells. He was elected to the American Association Advancement of Science for this “pioneering work on discovery of NK cells”.

He has served on the **US National Board of medical Examiners as test writer**, and he recently coauthored a report on competency-based education commissioned by AAMC/HHMI. He has played an active role in curricular reforms globally with special interest in his native India. He believes that technology can be a powerful democratizing force in medical education and is **developing innovative ways to use technology** for educating health science professionals.

TESTIMONIALS

“Ace The Board: Surgical Pathology Reimagined is truly a reimagined concept to study pathology. It is designed not only for those doing residency or applying for boards, but also for all of us already practicing. This book offers more than 4000 high-resolution photomicrographs accompanied by high-yield text, which is integrated with over 1000 whole slide images. This allows a really close to “real-pathology” experience. I genuinely believe every pathologist would have loved to have this book on their side during residency and for sure will enjoy it in day-to-day practice.”

VICTOR G. PRIETO, MD, PhD
Professor and Chair
Ferenc and Phyllis Gyorkey Chair for Research and Education in Pathology
Professor, Department of Dermatology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston TX, USA

“Wow! Ace the Boards: Surgical Pathology “Reimagined” is a GAME CHANGER. Beautiful high-quality images, high yield bullet point texts, useful algorithms, and tables, and scannable QR code links to virtual microscopic slides of numerous entities. This is a high yield, efficient, modern approach to learning & studying surgical pathology. Whether you are a new pathology trainee just starting out, a senior resident studying for boards, or a pathologist who needs a high yield reference for daily practice…this book is solid gold!”

JERAD M. GARDNER, MD
Dermatopathologist/Bone and Soft Tissue Pathologist
Section Head, Bone and Soft Tissue Pathology
Co-founder, Knowledge in Knowledge out
Deputy Editor, Archives of Pathology and Laboratory medicine
Geisinger Medical Center
Danville, PA, USA

“I can undoubtedly say that "Ace the Boards: Surgical Pathology Reimagined" is a pathology review book like none other. It focuses on high-yields facts with over 3000 histologic, gross, and immunohistochemical stain images and caters to variable learning styles as audio material, virtual slides and multiple-choice questions are part of the package. It is authored by people passionate for pathology and teaching. Authors/Editors include senior pathologists and also younger generation that have gone through the stress of boards preparation themselves not too long ago. It's a book of the future with QR codes linking to annotated digital whole scanned slides to enhance learning.
Truly, a book that I wish I had while I was preparing for my boards which is SUCCINT, FOCUSED and HIGH-YIELD!!”

ANIL PARWANI, MD, PhD, MBA
Professor of Pathology and Biomedical Informatics
Vice-Chair of Anatomic Pathology
Director of Pathology Informatics
Director, Digital Pathology Shared Resources
Principal Investigator, Cooperative Human Tissue Network (CHTN) Midwestern Division
Wexner Medical Center - Department of Pathology
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TESTIMONIALS

“Look forward to reading Ace the Boards: Surgical Pathology Reimagined, a new publication co-authored by Dr. Raj Singh, my co-editor of Digital Anatomic Pathology Academy (DAPA) of Digital Pathology Association (DPA). This book brings the traditional and digital board preparation material under one umbrella using over 1000 Path Presenter virtual slides. This is a much-needed supplementary resource for residents to study for the anatomic pathology board examination as well as for practicing pathologists to update their knowledge.”

MARILYN BUI, MD, PhD
Co-Editor of DAPA by DPA
Scientific Director of the Analytic Microscopy Core
Professor and the Director of the Cytopathology Fellowship
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“Ace The Boards Surgical Pathology “Reimagined” has an impressive display of surgical pathology images and descriptions that make the content comprehensive and digestible for studying. Having the option to easily access digital slides via QR codes along with a great flow of how the different branches of anatomical pathology are presented makes this a great investment for board studying and beyond.”

MICHAEL WILLIAMS, MD, MSc
Neuropathology fellow
University of Alabama at Birmingham
Birmingham, AL
Founder: Diversify in Path Podcast

“I must say, the more I read, more I love the book. Why could not we have it last year at the time of our board preparation? We were lost in the sea of resources and had to juggle between them trying to find out the best so that we don’t miss anything. This is such a comprehensive resource. Let it be the content or the concept of linking QR codes to the topics, it’s complete! Kudos to Akanksha for thinking about this concept and kudos to the team for coming up with this beauty.”

NIDHI KATARIA, MBBS
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New York, NY, USA

PREFACE

Commitment to excellence, collaborative learning, and innovation are the foundation of Ace my Path. Inspired by the overwhelmingly positive feedback on our prior books, we decided to commit to our biggest venture yet- to create a single comprehensive yet succinct surgical pathology learning resource for trainees and pathologists alike. Most of our team members are less than five years out of training; they can best see the limitations of the currently available resources and are most apt to create a new resource that is comprehensive.

During my board's preparation, I remember shuffling through my AP boards material in a hotel room in Tampa five days before the board's examination. Then, two days before the exam, my co-resident came in with his much more organized handwritten anatomic pathology notes. We went through his notes within a matter of hours; truly speaking, that was a very satisfactory experience. So, the inception of the idea of creating this book happened then.

Two years later, I came across Dr. Kurt Schaberg's Pathology Notes website, an online resource that succinctly discusses innumerable pathology entities based on organ systems and is very comprehensive. I couldn't wait to reach out to him for collaboration. We are passionate about learning and teaching and imagined a surgical pathology resource with lots of histologic, gross, and immunohistochemistry correlates. Pathology is best learned by seeing slides in addition to learning the material. This concept came to fruition when we collaborated with Dr. Rajendra Singh on Path Presenter. The concept of having high-yield notes on surgical pathology entities with digital links to whole scanned slide images was innovative. We knew this would revolutionize how surgical pathology is learned. Then, we started the task of turning this idea into a reality.

It was a huge undertaking, and in January 2022, we started to look for more dedicated team members who shared our goals and enthusiasm. We formed a strong, dedicated team of forty-two pathologists that contributed to different roles: editors, authors, reviewers, and path art contributors (not counting MCQ and video/audio content generators, who are currently working on it). A special mention for the Path Twitter-verse, where pathologists from all over the world contributed images of their rare cases out of dedication as teachers. They were an indispensable part of this project. This level of project did not come without challenges- many working hours after clinical duties, day and night meetings and brainstorming sessions, work delegation and implementation, and collaborative issues, to name a few. After ten months of extensive work, numerous drafts, and multiple reviews and edits, we present to you this product that is a one-of-a-kind immersive, innovative pathology learning experience.

This book is valuable for trainees and practicing pathologists. It contains organ-based high-yield information, including advances in the field. Key gross and photomicrographs for each entity accompanied by annotated virtual slides in Path Presenter is what distinguishes this book from all others. Our readers have access to a rich repository of images and more than 1000 virtual slides at the click of a button online or by scanning a QR code in the book, creating a seamless learning experience. Meanwhile, we are working on making video and audio files discussing the entities in the book. In addition, we will go over the virtual slides in those videos/audios. This will enhance the auditory learning experience, which is best for people on the go or away from their book or computer screen. However, that is not all; multiple-choice questions with virtual slides embedded in the questions and annotated explanations for the correct answers give the learners a true boards test experience. We think this book is a must-have for trainees in their board prep, but it also undoubtedly makes a great reference resource for practicing pathologists.

This book is a collaboration between the pioneers and the leaders of Pathology teaching, "Path Presenter," "Kurt's Notes," and "Ace My Path," and we've reconceptualized ("reimagined") the way of learning. We hope that our fruit of labor is beneficial to the readers. Finally, we wish you good luck and hope to be by your side in your surgical pathology learning journey.

- **AKANKSHA GUPTA, MD**
  Founder and CEO
  Ace My Path

ACKNOWLEDGEMENTS

“To God, for instilling a "purpose of life" in me. To my passionate mentors, for instilling in me the passion for Pathology. To my parents, Maya Gupta and Jugalkishore Gupta for instilling my values, my character, and for living a life that I can take inspiration from. To my loving husband, Ashish Gupta, for demonstrating going after one's ambition, for encouraging me to fulfill my dreams and pushing me every day to become my best self. And lastly, to my son and best friend, Siddharth Gupta, for reminding me every day that I matter, for being my biggest fan, and for sitting on my lap / hugging me (even while sitting on the computer to write this book), making me feel the warmth of his loving heart!”

- **AKANKSHA GUPTA, MD**

“To my wife, Manisha, daughter Kritika and son, Satyen who have selflessly sacrificed a lot and allowed me to follow my passions. To all my friends, mentors and colleagues who have been supportive and encouraging every step of the way.”

- **RAJENDRA SINGH, MD**

“To my family, Aiko, Ingrid, and Ben, for their love and patience. And also, to my mentors at Stanford for their inspiring teaching.”

- **KURT SCHABERG, MD**

“To my family: MaryAnn, Scott, Jamie, and Zachariah for all their support and love. A huge thank you to my group of mentors: Dr. Yi Ding, Dr. Sara E. Monaco, Dr. Jerad Gardner, and Dr. Andrew Campbell for all their support and wisdom over the years at Geisinger.”

- **TERRANCE LYNN, MD**

“This undertaking could not have been completed without the assistance of the Pathology Twitter verse, whose names may not be all enumerated here. Their contributions are sincerely appreciated and gratefully acknowledged. To my dearest husband, Shankar Sonawane, my beloved children Shree, Guru, and Dev, and my in-laws for their endless support, kind, and understanding spirit throughout the process of making this book. I am deeply grateful to my parents, Dr. Tulshiram and Poonam Shinde, my sister's Manswini, Trupti, my brother Ganesh, for their appreciation, encouragement, and a keen interest in my academic achievements. Above all, to the Great Almighty, the author of knowledge and wisdom, for his countless blessings.”

- **SNEHAL SONAWANE, MD**

“To my mentors and colleagues, both past and present, for their role in my professional growth and development. Thank you to my friends and family, who have always been there for me. A special dedication to my wife and best friend, Andi, for her constant support and unwavering love.”

- **JARED T. AHRENDSEN, MD, PhD**

“Thank you to all the collaborators! Special thanks to Akanksha Gupta for giving me this opportunity. You are inspiring!
To my wonderful family: Prabal, Mom, Dad, Akangsha, and Megha- Thank you for your unconditional love, support, and patience”

- **UPASANA JONEJA, MD**

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MULTIPLE CHOICE QUESTION MODULES

Authors to be added once live

VIDEOS

Authors to be added once live

OUTLINE

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ACE MY PATH
Come Ace With Us!

CHAPTER 1: APPROACH TO THE UNITED STATES AP/CP BOARD EXAMS

Nupur Sharma, MD
Hansini Laharwani, MD
Nidhi Kataria, MD
Akanksha Gupta, MD

APPROACH TO THE UNITED STATES AP/CP CERTIFICATION BOARD EXAMS

INTRODUCTION

This chapter will cover the following topics:

- Approach to AP/CP board exams
- Pre-exam requirements
- Preparation timeline and resources
- Post exam follow-up

PRE-EXAM REQUIREMENTS:

- Combined Anatomic Pathology and Clinical Pathology (AP/CP) Certification
- The applicant must have 48 months of full-time training in an accredited AP/CP program. Training must include at least 18 months each of structured AP and CP training. The remaining 12 months are flexible and may include AP and/or CP rotations
- Training may include up to 6 months of research during the pathology training program with the approval of the program director
- The applicant must have completed at least 30 autopsies by the time the application for certification is submitted.
- A list of completed autopsies must be uploaded with the application (see Appendix A: Autopsy Requirements)
- Candidates for combined AP/CP certification will not be certified by the ABPath until both the AP and the CP examinations are passed, and all requirements are met

APPLICATION:

THE AMERICAN BOARD OF PATHOLOGY

A Member Board of the American Board of Medical Specialties
AMERICAN BOARD OF PATHOLOGY
1936
Log in to PATHway
ABPath CertLink
PATHway: Create Username
Forgot Username / Password
SEARCH SITE
Search for...
Go!

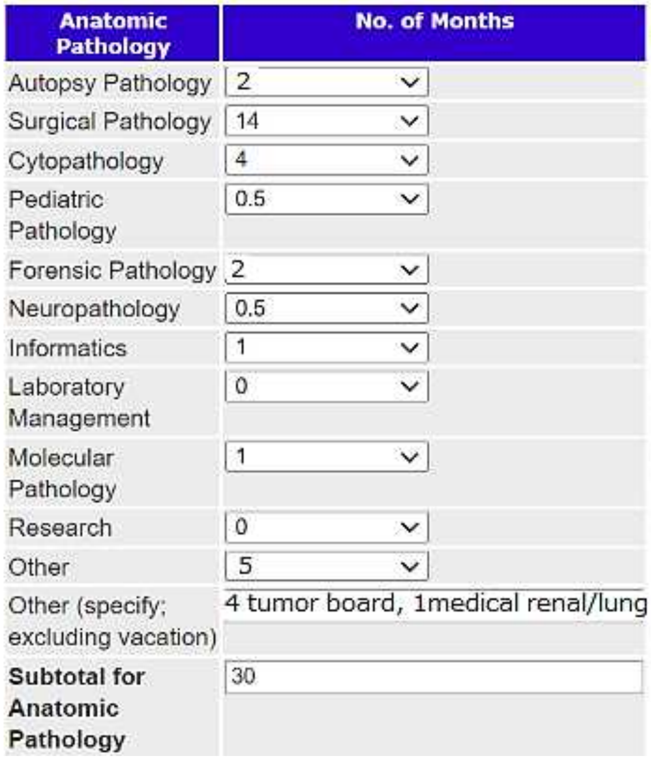
- Link: https://wds.dataharborsolutions.com/ABPathOrg/Default.aspx
- You will receive an email from ABPath about Board registration at the end of August
- Please keep your personal information up to date
- 2022 exam details:
  - Application Start 9/15/2021
  - Application Deadline 1/15/2022
  - Application Fee $2600 for AP/CP combined
  - Late submission deadline mid-February (costs additional $1050 (AP or CP only) or $1300 (combined AP/CP)
  - The window for scheduling exam: 3/9 – 5/2/2022
  - Exams will be administered : **5/16 – 6/3/2022**
- Schedule your exam date in March
- You will receive an email from ABPath for details

AUTOPSY LOG:

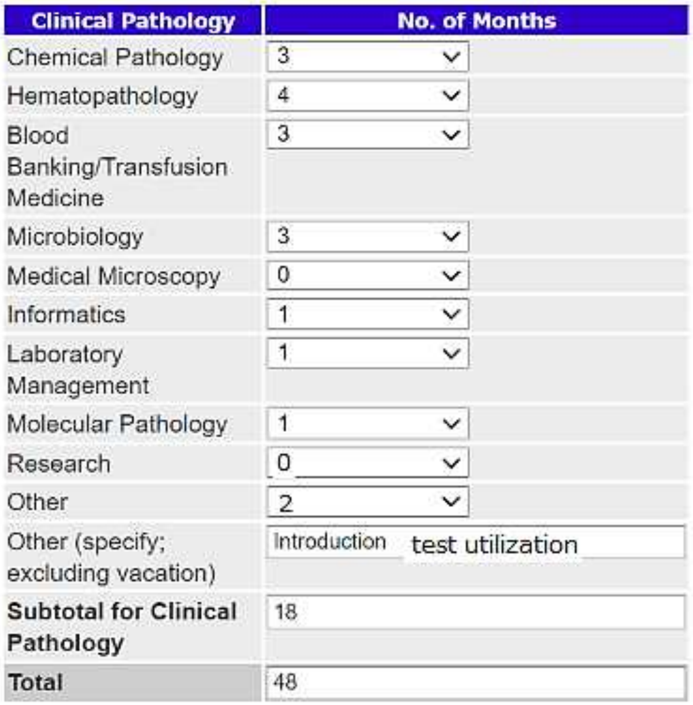
- Enter at least 30 cases with brief main diagnosis (cause of death)
- Link: https://apps.acgme.org/connect/login?returnUrl=https%3A%2F%2Fapps.acgme.org%2Fads%2F&redirect=True
- Export the Autopsy Log as PDF format
- The end product that goes in your application look like this

ROTATION LOG:

- Breakdown of weeks on AP & CP rotations



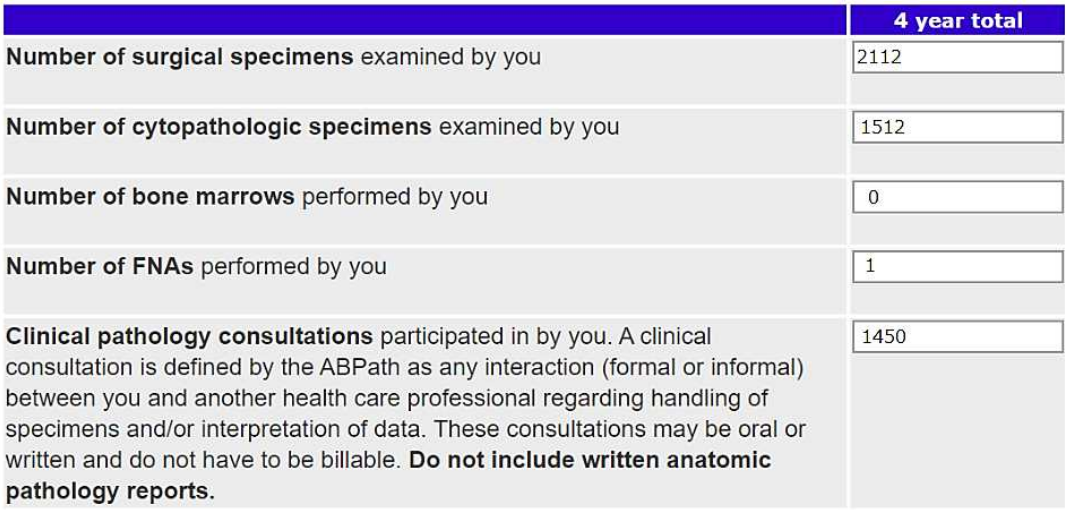
Anatomic Pathology	No. of Months
Autopsy Pathology	2
Surgical Pathology	14
Cytopathology	4
Pediatric Pathology	0.5
Forensic Pathology	2
Neuropathology	0.5
Informatics	1
Laboratory Management	0
Molecular Pathology	1
Research	0
Other	5
Other (specify; excluding vacation)	4 tumor board, 1medical renal/lung
Subtotal for Anatomic Pathology	30



Clinical Pathology	No. of Months
Chemical Pathology	3
Hematopathology	4
Blood Banking/Transfusion Medicine	3
Microbiology	3
Medical Microscopy	0
Informatics	1
Laboratory Management	1
Molecular Pathology	1
Research	0
Other	2
Other (specify; excluding vacation)	Introduction test utilization
Subtotal for Clinical Pathology	18
Total	48

CASE NUMBERS OF SURGICAL PATHOLOGY, CYTOPATHOLOGY, AND CLINICAL CONSULTATION

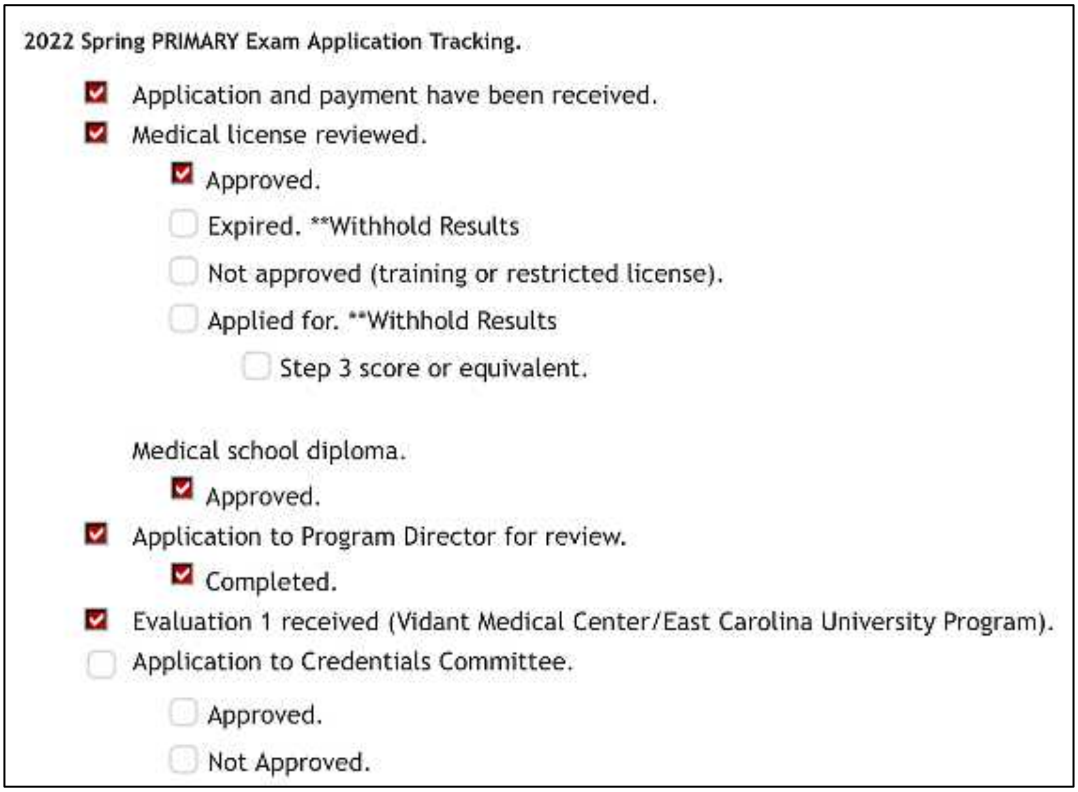
Clinical consultation includes Chemistry, Hematopathology, Blood bank, Tumor board, and CP on-call



	4 year total
Number of surgical specimens examined by you	2112
Number of cytopathologic specimens examined by you	1512
Number of bone marrows performed by you	0
Number of FNAs performed by you	1
Clinical pathology consultations participated in by you. A clinical consultation is defined by the ABPath as any interaction (formal or informal) between you and another health care professional regarding handling of specimens and/or interpretation of data. These consultations may be oral or written and do not have to be billable. **Do not include written anatomic pathology reports.**	1450

- Program Director must sign off that you have satisfactorily completed residency requirements
- After you submit your application, you will hear nothing for months. Be patient!

- You need following things in order to get your results: Remember to finish your full and unrestricted licensing!



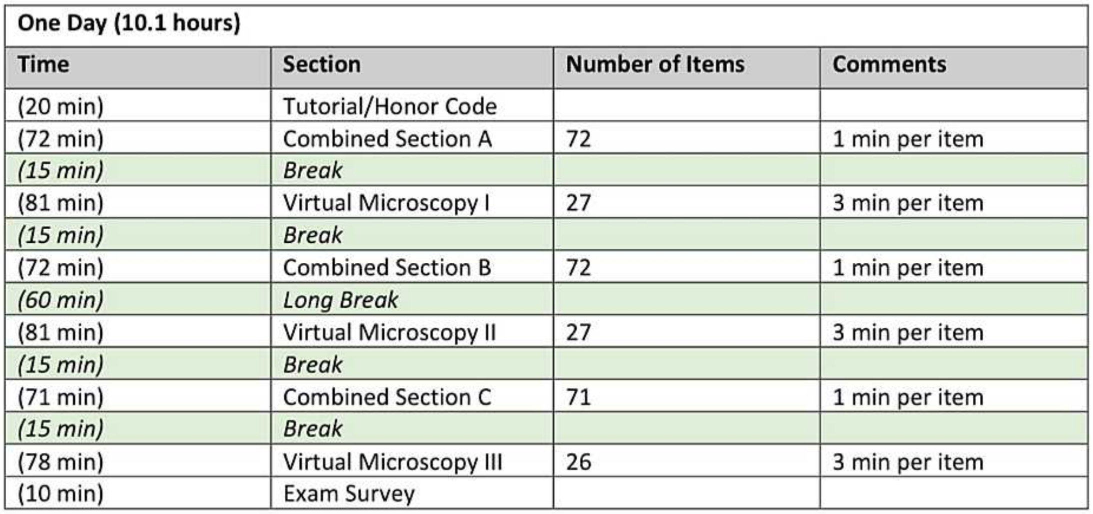
2022 Spring PRIMARY Exam Application Tracking.

- ☑ Application and payment have been received.
- ☑ Medical license reviewed.
  - ☑ Approved.
  - ☐ Expired. **Withhold Results
  - ☐ Not approved (training or restricted license).
  - ☐ Applied for. **Withhold Results
    - ☐ Step 3 score or equivalent.

Medical school diploma.

- ☑ Approved.
- ☑ Application to Program Director for review.
  - ☑ Completed.
- ☑ Evaluation 1 received (Vidant Medical Center/East Carolina University Program).
- ☐ Application to Credentials Committee.
  - ☐ Approved.
  - ☐ Not Approved.

SCHEDULE:
2022 AP BOARD EXAM SCHEDULE

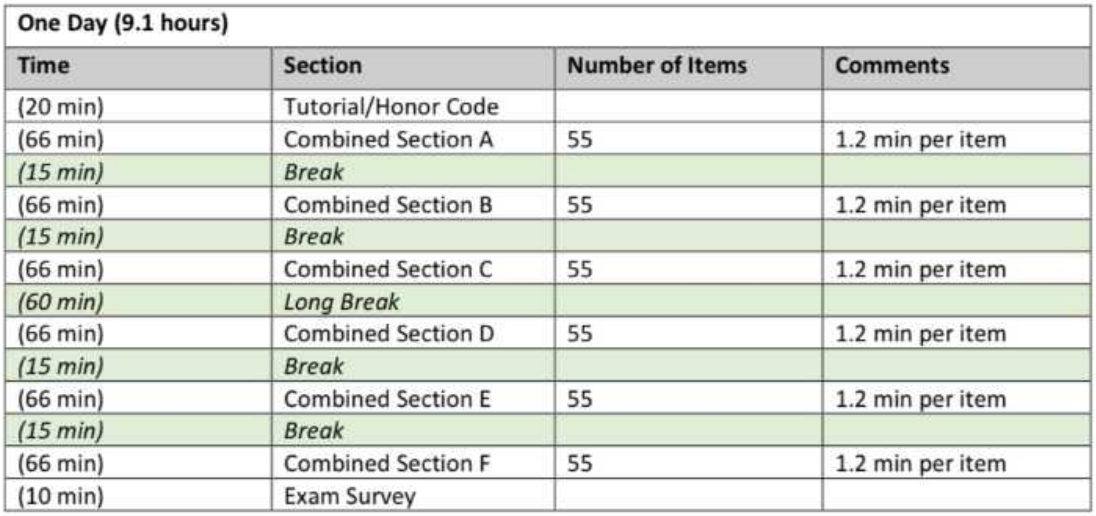


One Day (10.1 hours)

Time	Section	Number of Items	Comments
(20 min)	Tutorial/Honor Code		
(72 min)	Combined Section A	72	1 min per item
(15 min)	*Break*		
(81 min)	Virtual Microscopy I	27	3 min per item
(15 min)	*Break*		
(72 min)	Combined Section B	72	1 min per item
(60 min)	*Long Break*		
(81 min)	Virtual Microscopy II	27	3 min per item
(15 min)	*Break*		
(71 min)	Combined Section C	71	1 min per item
(15 min)	*Break*		
(78 min)	Virtual Microscopy III	26	3 min per item
(10 min)	Exam Survey		

- 3 multiple choice question sections, 215 questions (1 min/question)
- 3 virtual microscope sections, 80 questions (3 min/question)

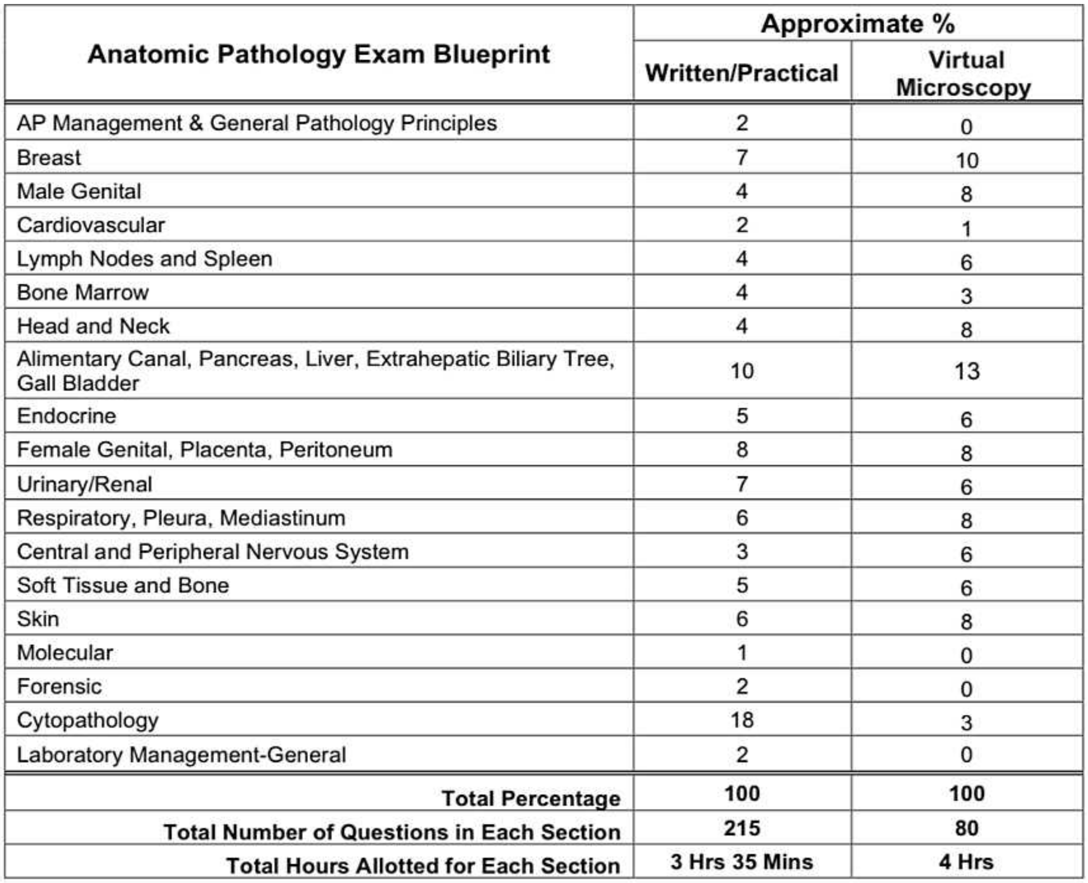
2022 CP BOARD EXAM SCHEDULE



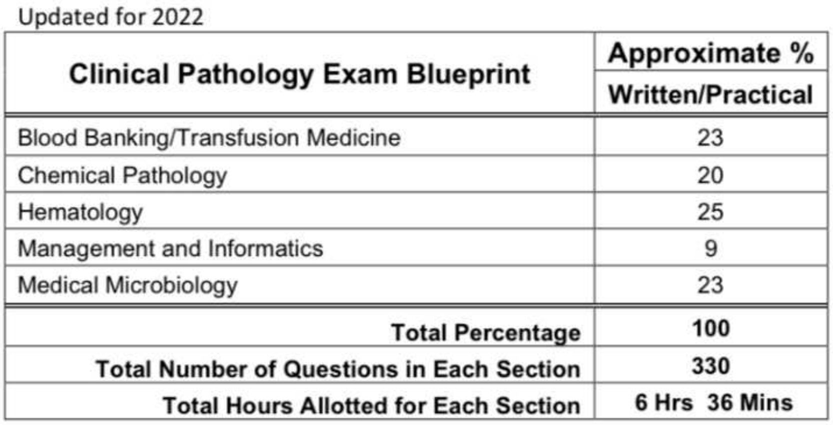
One Day (9.1 hours)			
Time	**Section**	**Number of Items**	**Comments**
(20 min)	Tutorial/Honor Code		
(66 min)	Combined Section A	55	1.2 min per item
(15 min)	*Break*		
(66 min)	Combined Section B	55	1.2 min per item
(15 min)	*Break*		
(66 min)	Combined Section C	55	1.2 min per item
(60 min)	*Long Break*		
(66 min)	Combined Section D	55	1.2 min per item
(15 min)	*Break*		
(66 min)	Combined Section E	55	1.2 min per item
(15 min)	*Break*		
(66 min)	Combined Section F	55	1.2 min per item
(10 min)	Exam Survey		

- 6 multiple choice question sections (1.2 min/question)
- 330 questions

EXAMINATION BLUEPRINT



Anatomic Pathology Exam Blueprint	**Approximate %**	
	Written/Practical	**Virtual Microscopy**
AP Management & General Pathology Principles	2	0
Breast	7	10
Male Genital	4	8
Cardiovascular	2	1
Lymph Nodes and Spleen	4	6
Bone Marrow	4	3
Head and Neck	4	8
Alimentary Canal, Pancreas, Liver, Extrahepatic Biliary Tree, Gall Bladder	10	13
Endocrine	5	6
Female Genital, Placenta, Peritoneum	8	8
Urinary/Renal	7	6
Respiratory, Pleura, Mediastinum	6	8
Central and Peripheral Nervous System	3	6
Soft Tissue and Bone	5	6
Skin	6	8
Molecular	1	0
Forensic	2	0
Cytopathology	18	3
Laboratory Management-General	2	0
Total Percentage	**100**	**100**
Total Number of Questions in Each Section	**215**	**80**
Total Hours Allotted for Each Section	**3 Hrs 35 Mins**	**4 Hrs**



Updated for 2022

Clinical Pathology Exam Blueprint	Approximate % Written/Practical
Blood Banking/Transfusion Medicine	23
Chemical Pathology	20
Hematology	25
Management and Informatics	9
Medical Microbiology	23
Total Percentage	**100**
Total Number of Questions in Each Section	**330**
Total Hours Allotted for Each Section	**6 Hrs 36 Mins**

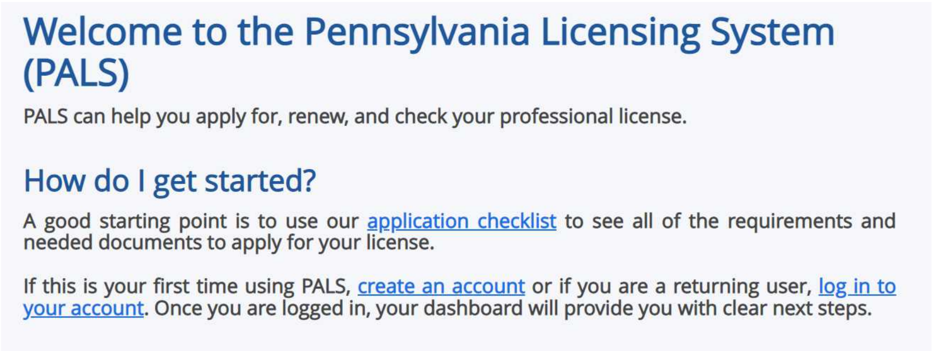
LICENSURE:

(Disclaimer: You don't have to get PA license, many residents in the past have gotten it, since it's easier and convenient; but feel free to choose a state license that is convenient as per your needs and future plans)

Full and Unrestricted Medical License Application

(**Pennsylvania** State)

- Fingerprints (FD-1164) $40
- Criminal record investigation (FBI) $18
- https://www.edo.cjis.gov/#/
- **Apply online, Pay online**. Mail fingerprint card
- You will receive an email link in a week
- Criminal record investigation (NC) $14
- https://ncsbi.gov/Services/SBI-Forms/SBIRight-to-Review__FILLABLE-2021.aspx
- Mail application, fingerprint card and money order together
- You will receive a letter in 2-3 weeks
- Go to the **Pennsylvania Licensing System (PALS)**
- (PALS.pa.gov) and create your account



Welcome to the Pennsylvania Licensing System (PALS)

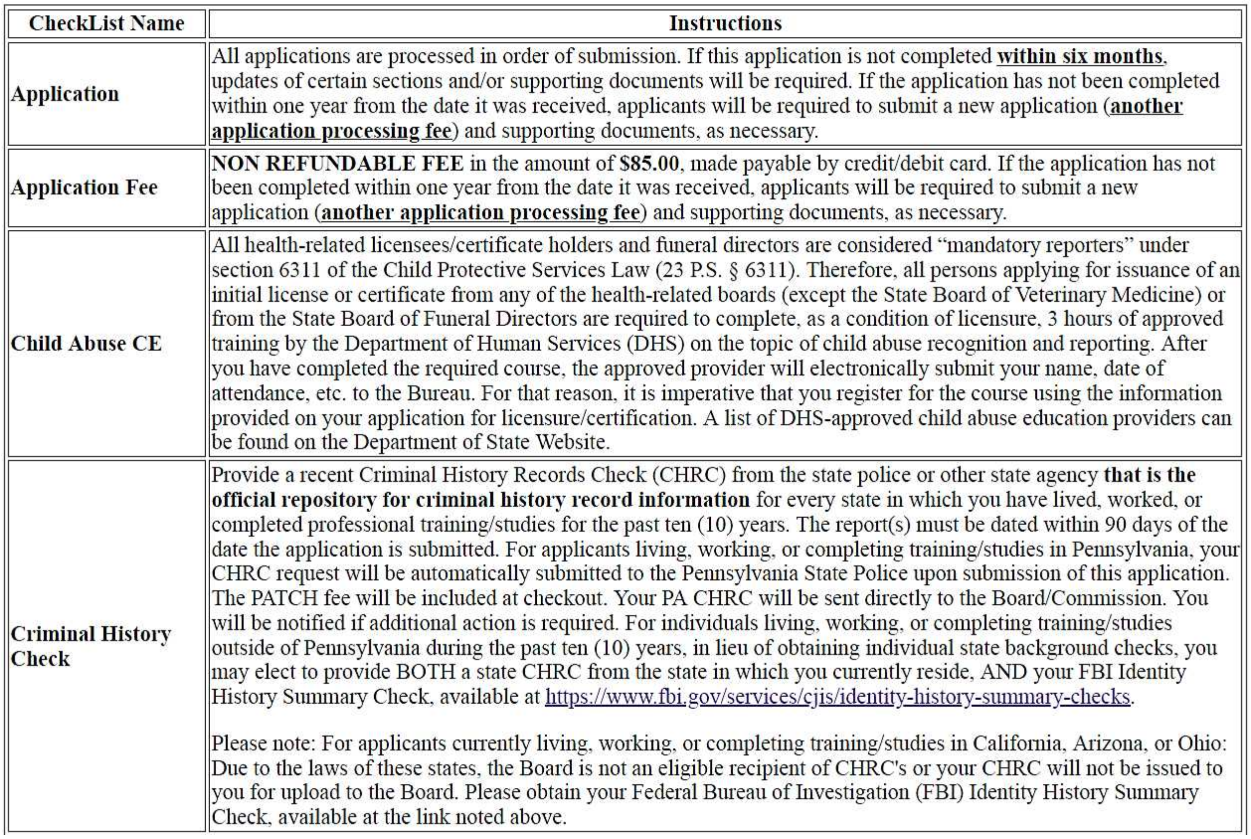
PALS can help you apply for, renew, and check your professional license.

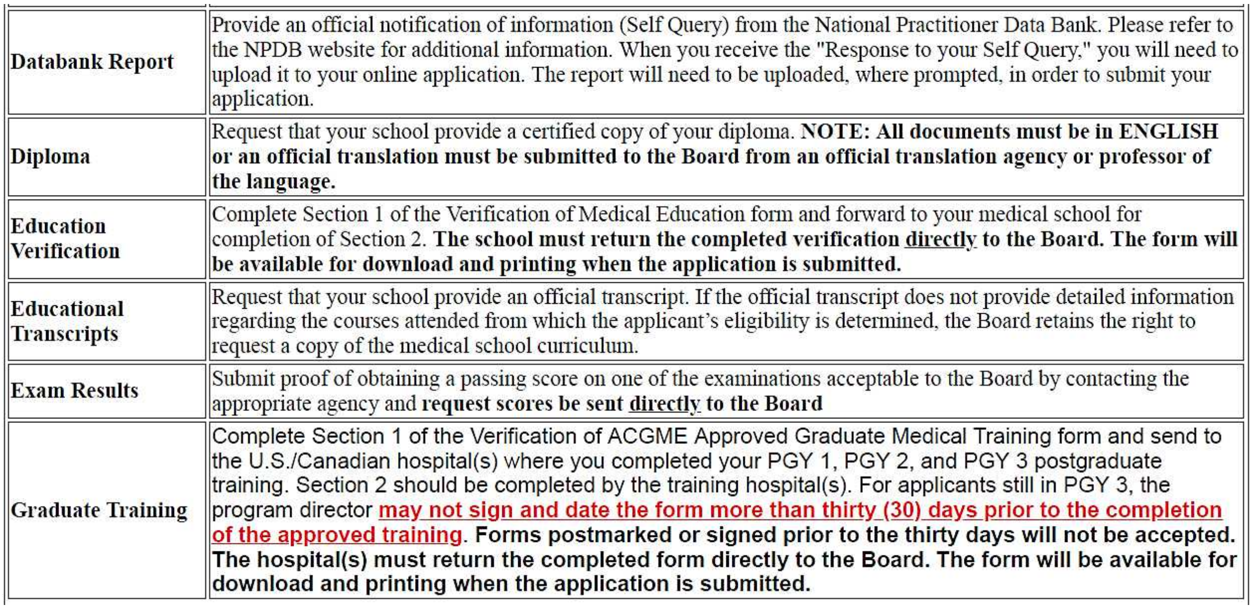
How do I get started?

A good starting point is to use our application checklist to see all of the requirements and needed documents to apply for your license.

If this is your first time using PALS, create an account or if you are a returning user, log in to your account. Once you are logged in, your dashboard will provide you with clear next steps.

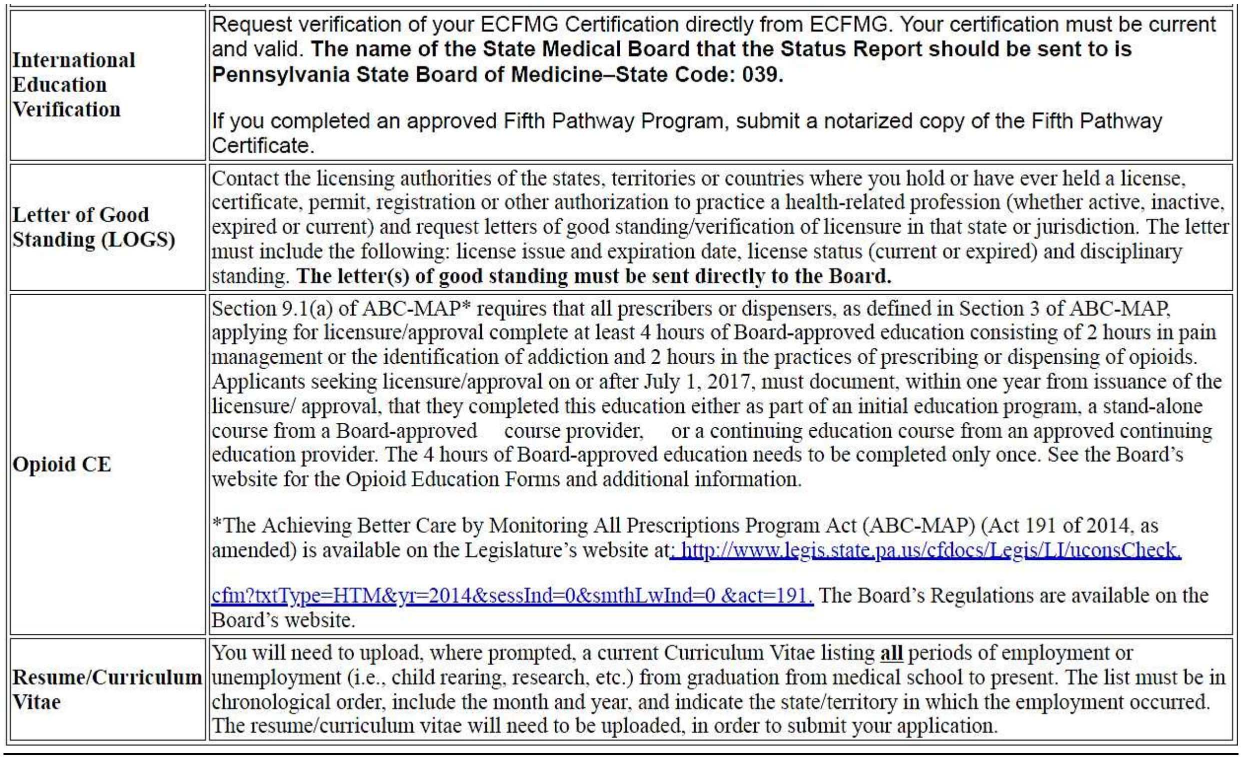
- Start application and pay $85 online
- Upload the following documents





CheckList Name	Instructions
Application	All applications are processed in order of submission. If this application is not completed **within six months**, updates of certain sections and/or supporting documents will be required. If the application has not been completed within one year from the date it was received, applicants will be required to submit a new application (**another application processing fee**) and supporting documents, as necessary.
Application Fee	**NON REFUNDABLE FEE** in the amount of **$85.00**, made payable by credit/debit card. If the application has not been completed within one year from the date it was received, applicants will be required to submit a new application (**another application processing fee**) and supporting documents, as necessary.
Child Abuse CE	All health-related licensees/certificate holders and funeral directors are considered "mandatory reporters" under section 6311 of the Child Protective Services Law (23 P.S. § 6311). Therefore, all persons applying for issuance of an initial license or certificate from any of the health-related boards (except the State Board of Veterinary Medicine) or from the State Board of Funeral Directors are required to complete, as a condition of licensure, 3 hours of approved training by the Department of Human Services (DHS) on the topic of child abuse recognition and reporting. After you have completed the required course, the approved provider will electronically submit your name, date of attendance, etc. to the Bureau. For that reason, it is imperative that you register for the course using the information provided on your application for licensure/certification. A list of DHS-approved child abuse education providers can be found on the Department of State Website.
Criminal History Check	Provide a recent Criminal History Records Check (CHRC) from the state police or other state agency **that is the official repository for criminal history record information** for every state in which you have lived, worked, or completed professional training/studies for the past ten (10) years. The report(s) must be dated within 90 days of the date the application is submitted. For applicants living, working, or completing training/studies in Pennsylvania, your CHRC request will be automatically submitted to the Pennsylvania State Police upon submission of this application. The PATCH fee will be included at checkout. Your PA CHRC will be sent directly to the Board/Commission. You will be notified if additional action is required. For individuals living, working, or completing training/studies outside of Pennsylvania during the past ten (10) years, in lieu of obtaining individual state background checks, you may elect to provide BOTH a state CHRC from the state in which you currently reside, AND your FBI Identity History Summary Check, available at https://www.fbi.gov/services/cjis/identity-history-summary-checks. Please note: For applicants currently living, working, or completing training/studies in California, Arizona, or Ohio: Due to the laws of these states, the Board is not an eligible recipient of CHRC's or your CHRC will not be issued to you for upload to the Board. Please obtain your Federal Bureau of Investigation (FBI) Identity History Summary Check, available at the link noted above.
Databank Report	Provide an official notification of information (Self Query) from the National Practitioner Data Bank. Please refer to the NPDB website for additional information. When you receive the "Response to your Self Query," you will need to upload it to your online application. The report will need to be uploaded, where prompted, in order to submit your application.
Diploma	Request that your school provide a certified copy of your diploma. **NOTE: All documents must be in ENGLISH or an official translation must be submitted to the Board from an official translation agency or professor of the language.**
Education Verification	Complete Section 1 of the Verification of Medical Education form and forward to your medical school for completion of Section 2. **The school must return the completed verification directly to the Board. The form will be available for download and printing when the application is submitted.**
Educational Transcripts	Request that your school provide an official transcript. If the official transcript does not provide detailed information regarding the courses attended from which the applicant's eligibility is determined, the Board retains the right to request a copy of the medical school curriculum.
Exam Results	Submit proof of obtaining a passing score on one of the examinations acceptable to the Board by contacting the appropriate agency and **request scores be sent directly to the Board**
Graduate Training	Complete Section 1 of the Verification of ACGME Approved Graduate Medical Training form and send to the U.S./Canadian hospital(s) where you completed your PGY 1, PGY 2, and PGY 3 postgraduate training. Section 2 should be completed by the training hospital(s). For applicants still in PGY 3, the program director may not sign and date the form more than thirty (30) days prior to the completion of the approved training. **Forms postmarked or signed prior to the thirty days will not be accepted. The hospital(s) must return the completed form directly to the Board. The form will be available for download and printing when the application is submitted.**

- If you have current ECFMG certification, you DO NOT need to request the record of graduation, educational transcript, and diploma from your medical schools



International Education Verification	Request verification of your ECFMG Certification directly from ECFMG. Your certification must be current and valid. **The name of the State Medical Board that the Status Report should be sent to is Pennsylvania State Board of Medicine–State Code: 039.** If you completed an approved Fifth Pathway Program, submit a notarized copy of the Fifth Pathway Certificate.
Letter of Good Standing (LOGS)	Contact the licensing authorities of the states, territories or countries where you hold or have ever held a license, certificate, permit, registration or other authorization to practice a health-related profession (whether active, inactive, expired or current) and request letters of good standing/verification of licensure in that state or jurisdiction. The letter must include the following: license issue and expiration date, license status (current or expired) and disciplinary standing. **The letter(s) of good standing must be sent directly to the Board.**
Opioid CE	Section 9.1(a) of ABC-MAP* requires that all prescribers or dispensers, as defined in Section 3 of ABC-MAP, applying for licensure/approval complete at least 4 hours of Board-approved education consisting of 2 hours in pain management or the identification of addiction and 2 hours in the practices of prescribing or dispensing of opioids. Applicants seeking licensure/approval on or after July 1, 2017, must document, within one year from issuance of the licensure/ approval, that they completed this education either as part of an initial education program, a stand-alone course from a Board-approved course provider, or a continuing education course from an approved continuing education provider. The 4 hours of Board-approved education needs to be completed only once. See the Board's website for the Opioid Education Forms and additional information. *The Achieving Better Care by Monitoring All Prescriptions Program Act (ABC-MAP) (Act 191 of 2014, as amended) is available on the Legislature's website at: http://www.legis.state.pa.us/cfdocs/Legis/LI/uconsCheck. cfm?txtType=HTM&yr=2014&sessInd=0&smthLwInd=0 &act=191. The Board's Regulations are available on the Board's website.
Resume/Curriculum Vitae	You will need to upload, where prompted, a current Curriculum Vitae listing **all** periods of employment or unemployment (i.e., child rearing, research, etc.) from graduation from medical school to present. The list must be in chronological order, include the month and year, and indicate the state/territory in which the employment occurred. The resume/curriculum vitae will need to be uploaded, in order to submit your application.

- FSMB (transcript directly to PA medical board) $70
- https://www.fsmb.org/transcripts/

ECFMG CERTIFICATION VERIFICATION SERVICE (CVS) ON-LINE $60

- https://secure2.ecfmg.org

OPIOID CE: https://www.train.org/pa/welcome

CHILD ABUSE CE: https://www.dos.pa.gov/ProfessionalLicensing/BoardsCommissions/Pages/Act-31.aspx

REGISTRATION:

- https://www.reportabusepa.pitt.edu//Login.aspx
- The online course will take four hours to finish
- Upload the certificate to PALS

RESOURCES AND TIMELINE:

Timeline for preparation:

- Start reading this book from the first year. This will go a long way!!
- Initial reading for boards: Approximately 2-3 hours of questions and text and 1 hour of group study per day starting in September
- January onwards: (6-7 hours per day), gradually increasing as time permits
- Recognize your strength and weakness early in 4th year
- Divide your time between reading text, doing questions and virtual slides each day to break the monotony
- Group study helps tremendously with understanding concepts and building recall ability. Ace My Path has developed many WhatsApp based groups for Pathologists and creates each year separate group for exam going residents. Contact us to be included in the groups

- Use flashcards for things like mutations in soft-tissue tumors
- Go through cases in your rotations and try to understand the etio-pathogenesis of diseases

Resources:

- AP: Kurt's notes, Board review courses, Path presenter high yield section with virtual images, one or more popular question banks (e.g., Pathdojo, PathPrimer, ASCP Question Banks etc.)
- What we have to offer:
  - Ace the boards: Surgical Pathology will give you a combined experience of question banks, notes, virtual slides, and videos all in one space
  - Contact us for buying a boards relevant annotated virtual slide hub, which has >1000 boards relevant virtual slides
  - In addition, videos/audios are available, which will go over our text and explain virtual slides
  - Multiple choice question module by Ace My Path consists of over 1500 board style questions, including questions with virtual microscopic slides
  - MCQs and videos will be rolled out within few months of release of this book. For more information, visit www.acemypath.com
- CP: CP compendium, CDC (microbiology images), selective reading- Henry's, popular question banks (e.g., Spitalnik, Pathdojo)
- Our other boards relevant resources include:
  - Ace the boards: Neoplastic Hematopathology
  - Ace the boards: Non-Neoplastic Hematopathology and Coagulation
  - Ace the boards: Cytopathology

EXAM DAY:

- The day: Try to stay relaxed!!!! (Easier said than done 😊)
- The exam is currently being conducted at Pearson-VUE exams enters, and information is available on the ABPath website as well as on the link below
- Reach the center well before time and bring 2 identity proofs with you. Get light snacks (e.g., Banana, yogurt, chocolate, peanut sandwich, coffee, water bottle, coke etc. Bring lunch if you can, it will save your time and you can relax more in your lunch break). Sometimes, the exam center buildings have cafeteria, but it is good to have some snacks for the small breaks
- For the exam, first and foremost in the tutorial session make sure virtual slides and images are working well. If not, please contact the proctor ASAP
- Preferably, follow the exam format as provided by ABPath, taking all the breaks to refresh your minds in between different sessions
- Try to stay focused and relaxed, getting through last 2 sessions can become challenging
- Use your system from Med School/Steps – flag questions, use scratch paper, choose an answer and don't look back
- Instructions and test interface are super straightforward; REALLY, NO ONE IS TRYING TO TRICK YOU
- Time allotted is adequate
- You may come across diagnoses you've never heard of – and that's okay, happens to the best of us!
- Odd clinical factoids you don't know about common entities can be encountered
- Best way to prepare for this is to stay engaged during residency
- Senior year is a good time to go over weak areas (sit in on sign outs and pay attention!)
- Focus on Hematology and Coagulation, as they are high yield as well. Do lots of morphology for heme
- Follow ABPath's blueprint for system wise distribution of questions and their weightage. Our book is created keeping the blueprint in mind
- As per their website, board passing rate is >90% for both AP and CP. So, work hard and smart and stay relaxed

Test center information:
American Board of Pathology (abpath.org)

POST-EXAM FOLLOW UP:

- Results are available usually in 8 weeks, so look out for the email from ABPath. Again, keep your email updated on ABPath website to receive your results
- Most important: Don't give away this book to juniors after boards, you will benefit hugely with it while starting to practice as well!

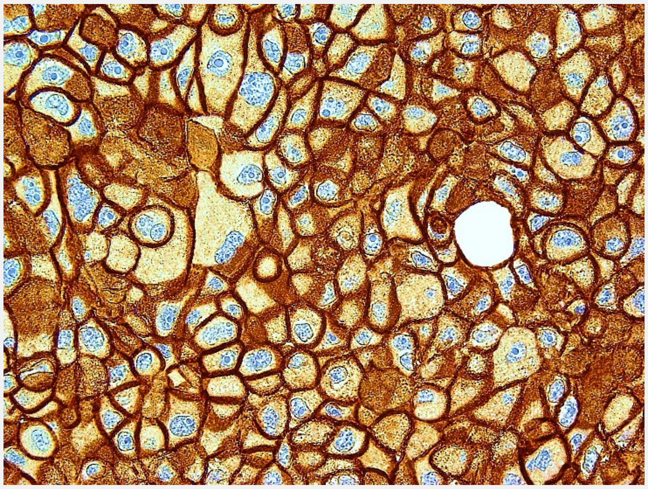
Disclaimer: While the authors believe that the information stated in this chapter is correct and current for 2022 to the best of their knowledge, applicants are requested to verify all information before use. The authors claim no responsibility for any change/update in the above-mentioned data.

ALL THE BEST FOR YOUR BOARDS AND PATHOLOGY CAREER!! COME ACE WITH US!!

ACE MY PATH TEAM

References:

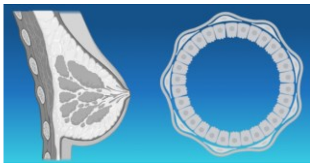
- Abpath.org
- PALS.pa.gov



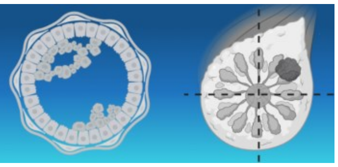
HER-2 Immunostain, invasive ductal carcinoma of the breast. Image courtesy: Takashi Fujisawa, MD, Ph.D. (@Patholwalker)

CHAPTER 2: BREAST PATHOLOGY

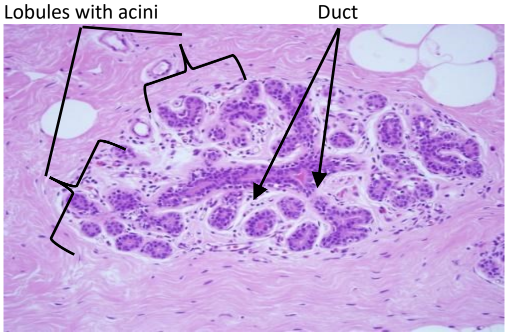
Terrance Lynn, MD
Aastha Chauhan, MD
Pukhraz Basra, MD
Akanksha Gupta, MD
Jian Li, MD

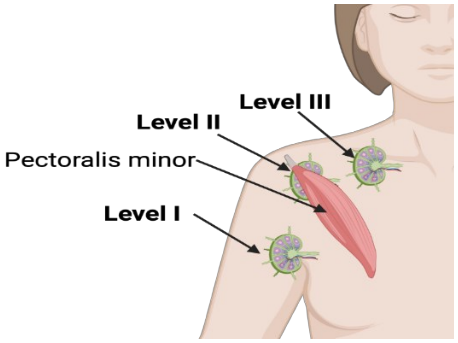


2. BREAST PATHOLOGY



NORMAL ANATOMY





Created by Dr. Terrance Lynn using BioRender.com

NORMAL BREAST PARENCHYMA

STRUCTURE

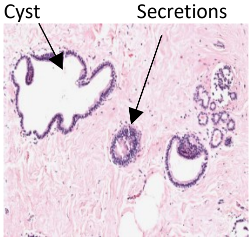
- Breast parenchyma is composed of terminal duct lobular units (TDLU)
- Variable amounts of adipose present, as age increases → adipose increases
- TDLU is composed of acini, dense connective tissue, loose connective tissue, and Cooper's ligament
- Milk originates in lobules and travels to mammary ducts to lactiferous sinuses to lactiferous ducts, and is excreted out of the nipple
- Acini and duct network → Composed of outer myoepithelial cells and inner cuboidal-columnar epithelial cells

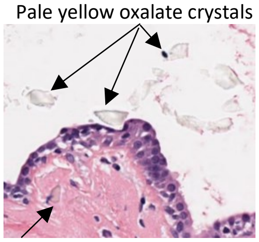
OTHER HIGH YIELD POINTS

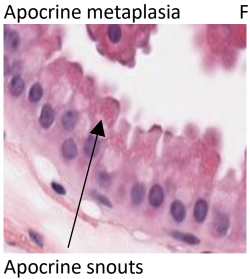
- Myoepithelial cells IHC: Positive for **calponin, p63, CK5/6, S100**, actin
- Ductal epithelium IHC: **Cytokeratin**

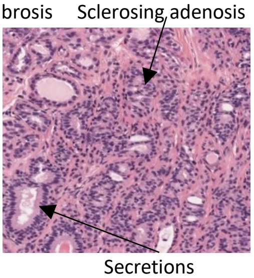
Breast Lymph Node Levels	
Level I	Located at the **lateral border of pectoralis minor** Has an anterior (pectoral axillary), posterior (subscapular axillary), and lateral (humeral) groups
Level II	Centrally located and are **deep to pectoralis minor** Central axillary and some apical axillary lymph nodes
Level III	**Medial to pectoralis minor** Composed of interpectoral lymph nodes (Rotter's Nodes) and the majority of apical axillary lymph nodes

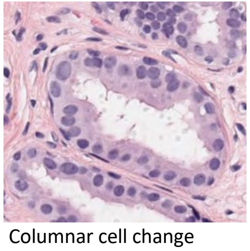
REACTIVE AND BENIGN EPITHELIAL LESIONS

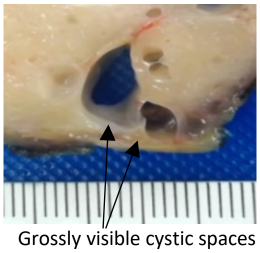












NON-PROLIFERATIVE CHANGES (FIBROCYSTIC CHANGES)

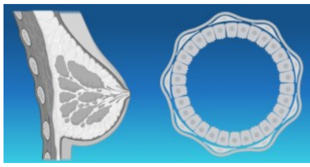
MORPHOLOGY

- **Cysts** are lined by a **single layer of epithelial cells** with outer myoepithelial cells, and the lumen may contain **calcifications, secretions**, or foamy histiocytes
- **Stromal fibrosis** commonly **surrounds the cyst wall** and can be exaggerated upon repeated cyst ruptures, inflammation, and lead to scarring
- **Apocrine metaplasia** shows eosinophilic ductal epithelial cells with **apical snouts, round nuclei with conspicuous nucleoli**; cysts may contain oxalate crystals but are challenging to see on H&E due to being pale yellow or colorless
- **Columnar cell change** shows cells that are **perpendicularly oriented** to the basement membrane and **round nuclei** and occasionally conspicuous nucleoli, and pale eosinophilic to amphophilic cytoplasm
- **Increased acini per lobule define adenosis**, and they are often columnar and seen in **pregnant women**; they may have stromal fibrosis, especially after rupture

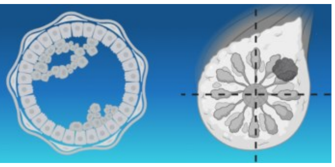
OTHER HIGH YIELD POINTS

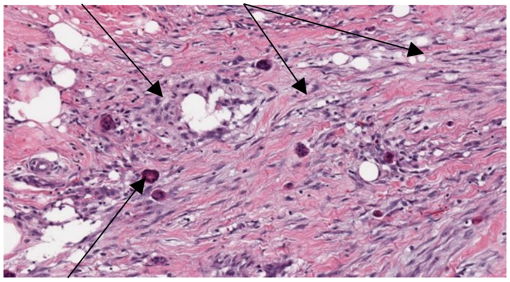
- **Most common non-proliferative lesion** of the breast
- **No significant** increased **risk** of cancer
- Pathogenesis: Excess hormone secretion
- **Risk factors:** Late age menopause (**prolonged estrogen exposure**), hormonal replacement therapy, **nulliparity**, and **low BMI**

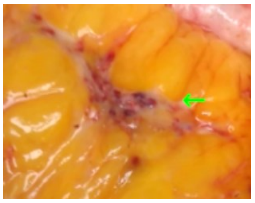
Path Presenter



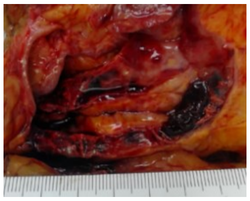
2. BREAST PATHOLOGY



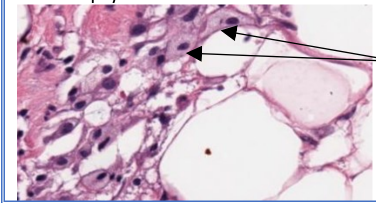

Fat necrosis
Fibrosis
Giant cells



Core Biopsy Site



Excisional Biopsy Cavity


Foamy histiocytes
Fat necrosis

BIOPSY SITE CHANGE

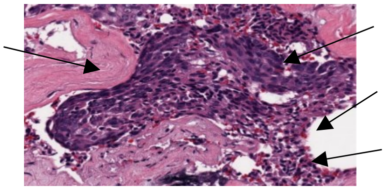
MORPHOLOGY

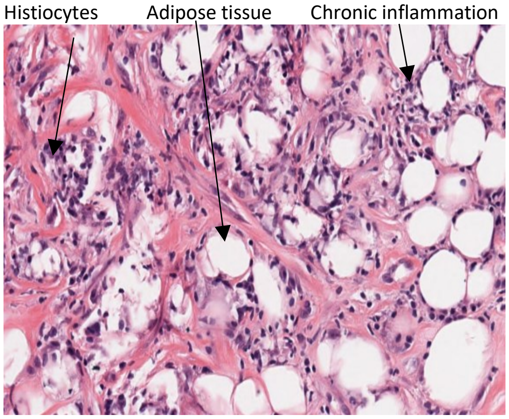
- **Organizing hemorrhage** (with hemosiderin-laden macrophages and blood)
- **Fat necrosis** (with foamy macrophages)
- Foreign body **giant cells** and/or foreign material, **granulation tissue, fibrosis**
- Acute and chronic **inflammation**
- **Squamous metaplasia**
- "**Epithelial displacement**" of ductal epithelium

OTHER HIGH YIELD POINTS

- **Pitfall warnings:**
  - ➢ Post-biopsy, there can be "**epithelial displacement**" where epithelium (benign or atypical) can be found within the stroma or vascular spaces
  - ➢ Epithelial displacement is **more common in papillary lesions,** which can result in an **erroneous diagnosis of invasive carcinoma**
  - ➢ When the epithelial fragments are **confined to the biopsy site**, a diagnosis of epithelial displacement should be favored
  - ➢ A diagnosis of **invasive carcinoma** should only be made if epithelium is found in the stroma **away from the biopsy site**

Path Presenter


Fibrosis
Squamous metaplasia
Hemorrhage
Inflammatory cells


Histiocytes
Adipose tissue
Chronic inflammation

FAT NECROSIS

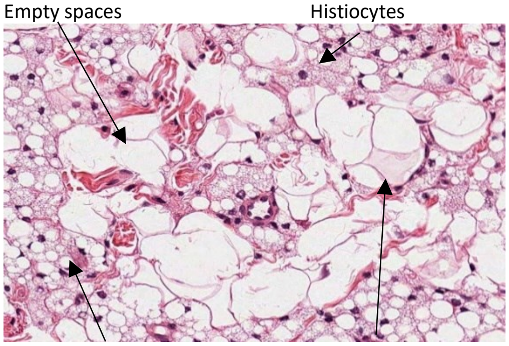
MORPHOLOGY

- **Necrotic adipose tissue** characterized by cystic spaces surrounded by lipid-laden ("**foamy**") **macrophages**
- **Variable** acute and chronic **inflammation**
- **Early** stage → **hemorrhage** and **histiocyte** reaction
- **Late** stage → **fibroblastic proliferation** and **collagen** deposition

OTHER HIGH YIELD POINTS

- Can **mimic malignancy** clinically and/or radiographically
- Occurs secondary to **injury** following surgery, biopsy, or **trauma**
- IHC: **CD68** positive histiocytes

Path Presenter


Empty spaces
Histiocytes
"Swiss cheese" holes
Pale amorphous material

REACTIONS TO FOREIGN MATERIAL

SILICONE GRANULOMA

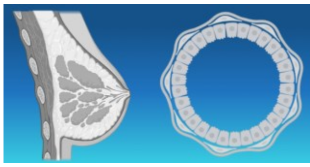
MORPHOLOGY

- Many **oval** and **empty spaces** ("**Swiss cheese**") may or may not contain pale **amorphous material**
- Adjacent **histiocytes/giant** cells reacting to the polydimethylsiloxane

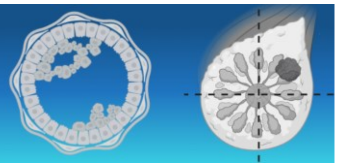
OTHER HIGH YIELD POINTS

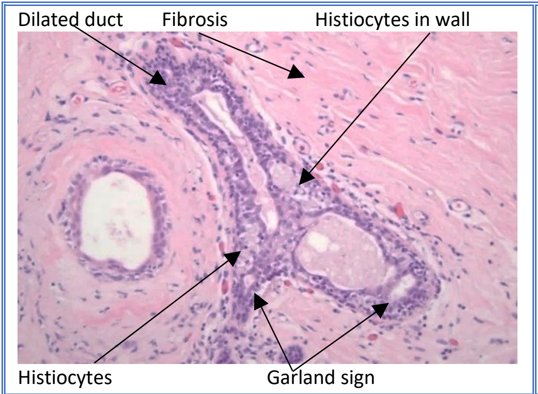
- Silicone leakage can be **seen even without frank** implant **rupture**
- Newer silicone implants have **liquid** silicone (at body temperature), which can **migrate locally and distantly**

Path Presenter



2. BREAST PATHOLOGY




Dilated duct
Fibrosis
Histiocytes in wall
Histiocytes
Garland sign

DUCT ECTASIA

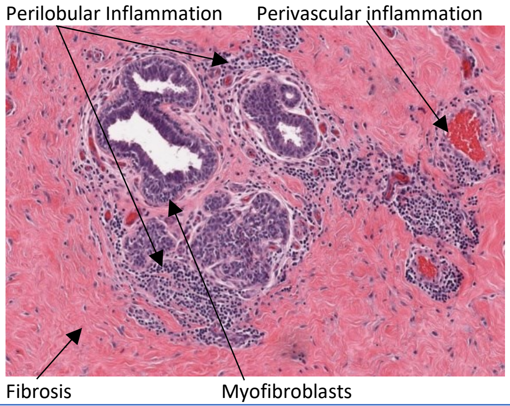
MORPHOLOGY

- Varying amounts of **periductal chronic inflammation**, **fibrosis**, and duct **dilation**
- Inspissated **lipid-rich material**, with **foamy macrophages** that often infiltrate the wall
- May have **squamous metaplasia** or **"Garland" sign** (obliterated duct lumen with recanalization around the periphery of ducts by small tubules)

OTHER HIGH YIELD POINTS

- Primarily **perimenopausal and post-menopausal** women
- Can present with pain, discharge, mass, or calcification

Path Presenter


Perilobular Inflammation
Perivascular inflammation
Fibrosis
Myofibroblasts

DIABETIC MASTOPATHY

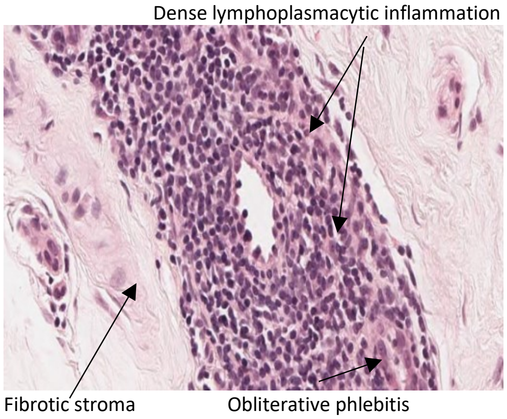
MORPHOLOGY

- Dense, **keloid-like fibrosis** with **epithelioid myofibroblasts** in stroma
- Periductal, perivascular, and perilobular **lymphocytic infiltrates** containing predominantly **B-cells**

OTHER HIGH YIELD POINTS

- **Fibroinflammatory** breast lesion, which presents as a **dense breast mass** and is **often bilateral**
- Characteristically presents in **premenopausal women** with long-standing **type 1 diabetes mellitus** and can be recurrent
- It can be **seen with other autoimmune** disorders (Grave's, Hashimoto, Pernicious anemia, SLE, RA, etc.) and in men
- IHC: **CD20 (+) B-Cells**

Path Presenter


Dense lymphoplasmacytic inflammation
Fibrotic stroma
Obliterative phlebitis

IgG4 RELATED MASTITIS

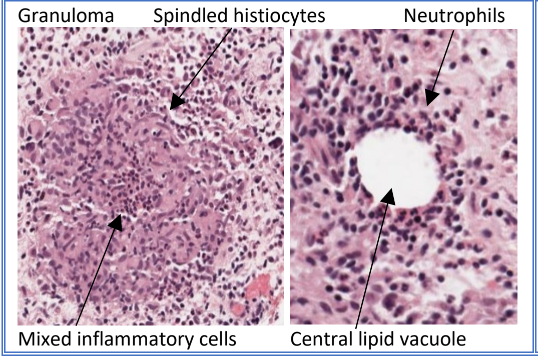
MORPHOLOGY

- Dense **lymphoplasmacytic infiltrate** in a fibrotic stroma with **storiform pattern** and **obliterative phlebitis**
- The absence of neutrophils, granulomas, and giant cells is essential

OTHER HIGH YIELD POINTS

- Can have **bilateral involvement** of the breast and **lymphadenopathy**
- Occurs in middle-aged females; ~50% have **hypocomplementemia**
- May have substantial **weight loss** or **peripheral eosinophilia**
- Other organs are often involved at the time of diagnosis
- IHC: Increased **IgG4 positive plasma cells (>40% IgG4/IgG ratio)**

Path Presenter


Granuloma
Spindled histiocytes
Neutrophils
Mixed inflammatory cells
Central lipid vacuole

GRANULOMATOUS MASTITIS

MORPHOLOGY

- Nonspecific **lobulocentric** granulomatous inflammation with epithelioid and spindled histiocytes, multinucleated **giant cells**, and a **central lipid vacuole**
- Often will have neutrophils, lymphocytes, plasma cells, and eosinophils

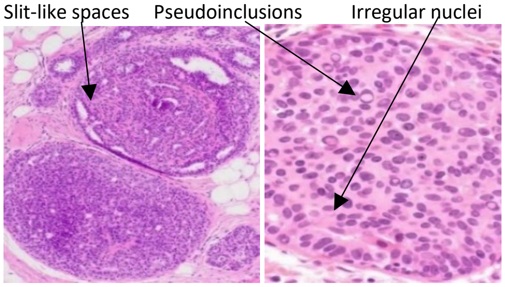
OTHER HIGH YIELD POINTS

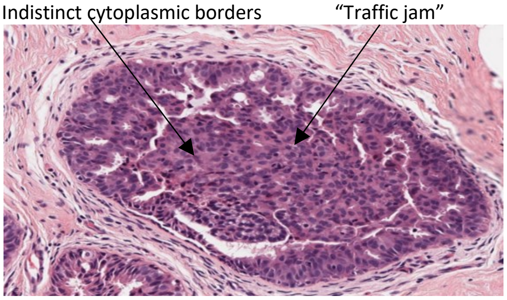
- It can be seen in certain **Corynebacterium infections**
- Other considerations: **Sarcoidosis**, prior procedure site changes, infection, and idiopathic

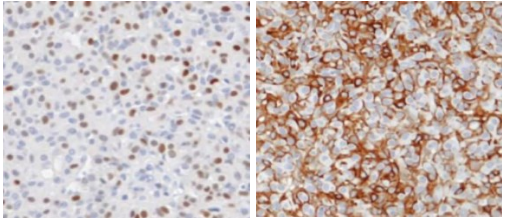
Path Presenter

2. BREAST PATHOLOGY

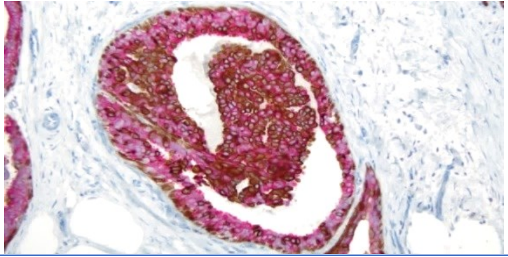
BENIGN EPITHELIAL LESIONS AND PRECURSOR LESIONS






ER "on-off" pattern

CK5/6 (HMWK)


BNC-5 showing polyclonal keratin expression

USUAL DUCT HYPERPLASIA (UDH)

MORPHOLOGY

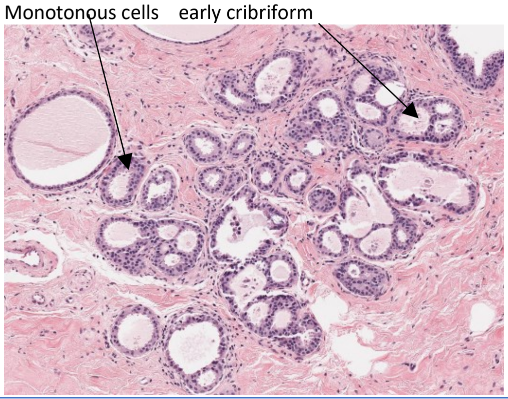
- A **cohesive proliferation** of epithelial cells arranged in **a haphazard architecture** with irregular, **slit-like spaces**, often peripherally located
- **Epithelial cells** are variably sized cells with **indistinct borders**, **overlapping nuclei** with frequent **nuclear grooves**, and some **pseudoinclusions**
- **Any bridges are thin** and stretched with **"traffic jam"** type pattern
- **Any micropapillae** have broad bases and **narrow tips** with small pyknotic nuclei

OTHER HIGH YIELD POINTS

- Epithelial cells stain with a **mixture** of **low molecular-weight** (e.g., CK7) and **high-molecular weight cytokeratins** (e.g., CK5/6)
- **BNC-5 stain** will show brown staining for p63 (nuclear) and brown cytoplasmic CK903, and cytoplasmic red CK7 and CK8/18 staining
- **Heterogeneous ER staining** pattern: **Some are "on," others are "off"**
- Confers approximately a **2-fold increased risk for breast cancer**

UDH	DCIS
Think: Polyclonal	**Think: Monoclonal**
Irregular, slit-like lumina, often peripheral	Regular, punched out lumina, often central
Streaming architecture	**Prominent polarization** around lumina
Variation in cell size/shape	Monomorphic cells/shape
Indistinct cell margins	**Distinct cell margins**
Admixture of cell types (epithelial, myoepithelial and/or apocrine): Stain with high and low-molecular weight cytokeratins	Proliferating cells are epithelial. Myoepithelial cells are against the basement membrane: Epithelium stains with low-molecular weight cytokeratins only
Heterogenous ER staining (think: "some on, some off")	Strong, diffuse ER staining (think: "all on")
CK5/6 positive	CK5/6 negative

Path Presenter



ATYPICAL DUCT HYPERPLASIA (ADH)

MORPHOLOGY

- **Neoplastic proliferation** of **evenly spaced epithelial cells** with round nuclei, dense chromatin, arranged in **cribriform architecture**, **bridging** or **micropapillae**

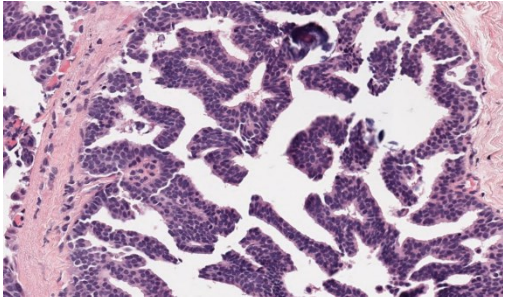
OTHER HIGH YIELD POINTS

- Confers a **4 to 5-fold relative risk for breast cancer**
- **Size: ≤2mm and <2 duct spaces**; otherwise, it is DCIS
- Findings that **increase the likelihood of malignancy**: **multiple foci** of ADH, **marked nuclear atypia**, or **micropapillary** architecture
- Treatment: On biopsy → surgical excision to exclude DCIS/invasive; Found on excision → no additional treatment
- IHC: High ER (+) expression

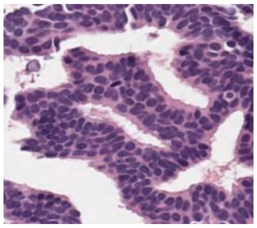
Path Presenter

LOW-GRADE DCIS

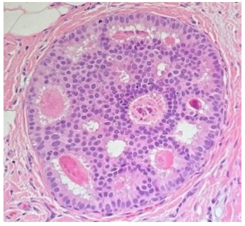
Micropapillary



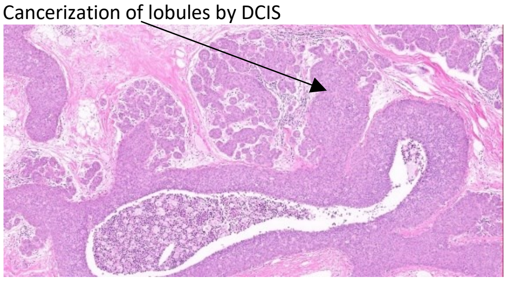
Polarization



Cribriform pattern



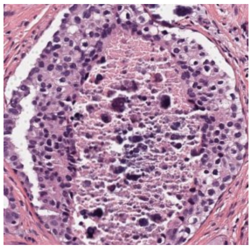
Cancerization of lobules by DCIS



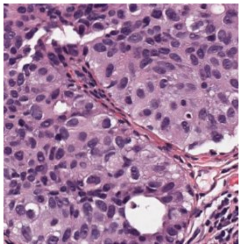
Picture courtesy: Lorand Kis, MD

HIGH-GRADE DCIS

Comedo necrosis

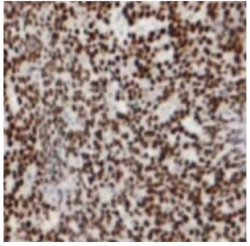


Pleomorphism

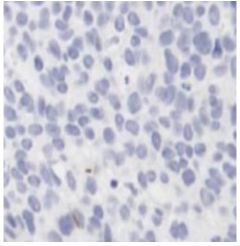


IMMUNOHISTOCHEMISTRY

ER “Clonal pattern”



CK5/6 Negative



DUCTAL CARCINOMA IN SITU

MORPHOLOGY

- Neoplastic proliferation of epithelial cells of **ductal origin**
- **Morphologic** appearance **defines the grade** (not architecture)
- Nuclei can be round to oval, have regular or irregular nuclear contours, and conspicuous or inconspicuous nucleoli

OTHER HIGH YIELD POINTS

- Often limited to one duct system but can involve the lobules and is specifically called “**cancerization of lobules**”
- No specific size requirement is needed (unlike ADH)
- Majority are non-palpable and thus usually detected on mammography with associated with **linear calcifications** which are microcalcifications
- **Relative risk** of **invasive cancer** in ipsilateral breast is **~10 X**
- Approximately 40% of low-grade lesions progress to invasive carcinoma if left untreated
- High-grade lesions often associated with stromal reaction with fibrosis, sclerosis, or infiltrative lymphocytes
- **Graded** based **on nuclear morphology**
  - ➢ **Low grade:** Think “**small bland**” monomorphic cells
  - ➢ **Intermediate grade:** Features between low and high-grade
  - ➢ **High-grade: T**hink “**ugly and pleomorphic**” cells
- Treatment: Excision with “wide” negative margins; +/- radiation therapy and/or hormone therapy
- IHC: Dependent on grade, but **ER/PR is positive** in a **clonal** pattern, HER2 is variable (HER2 not performed on in situ), negative for CK5/6; myoepithelial cells are positive for p40, p63, CK5/6. E-Cadherin retained (Lost in LCIS)
- Molecular: **PIK3CA** (~25%), **TP53** (10-15%), **GATA3** (~10%) mutations
- Cytogenetics:
  - ➢ **Low grade:** Chromosomal **losses** in **16q, 17p**, and **gains** at **1p**
  - ➢ **High grade:** Chromosomal **losses** at **8p, 11q, 13q, 14q**, and **gains** at **5p, 8q, 17q**

Low-grade DCIS	High-grade DCIS
Small monomorphic cells 1.5-2x size of RBCs Regular nuclear contours Even chromatin Small to inconspicuous nucleoli	**Large, pleomorphic cells** >2.5x size of RBC Irregular nuclear contours Coarse chromatin Prominent nucleoli
Usually **cribriform** or **micropapillary** growth	Usually **solid** growth, but may have any architectural pattern
Polarization around lumina	**No polarization** around lumina
Necrosis **uncommon**	Necrosis **common**, especially comedo
Must be >2mm and **involve more than 2** complete spaces	**No size** requirement
ER and PR **positive** (frequently)	ER and PR **negative** (more frequently)
HER2 is **negative** (frequently)	HER2 is **positive** (frequently)
Few mitoses	**Many** mitoses
Low-grade associated cancers	High-grade associated cancers

BNC-5 stain demonstrating retained myeopithelial cells (nuclear p63, cytoplasmic CK5/6; brown stain) and clonal luminal cytokeratin expression (CK8/18)

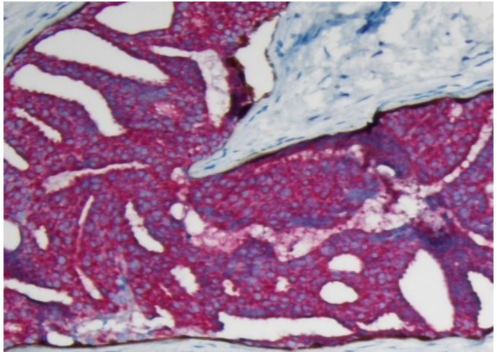
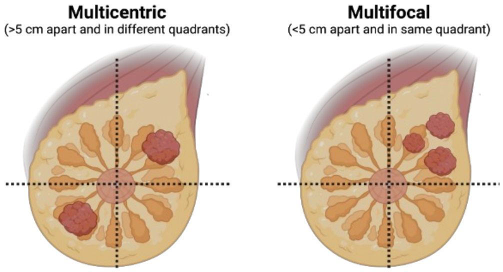
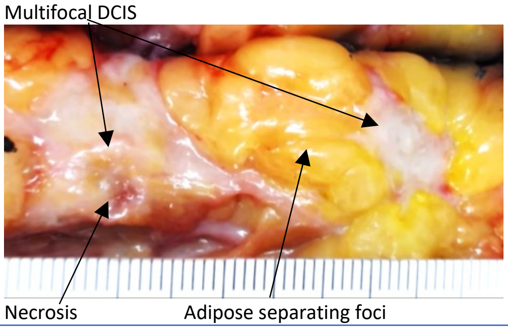
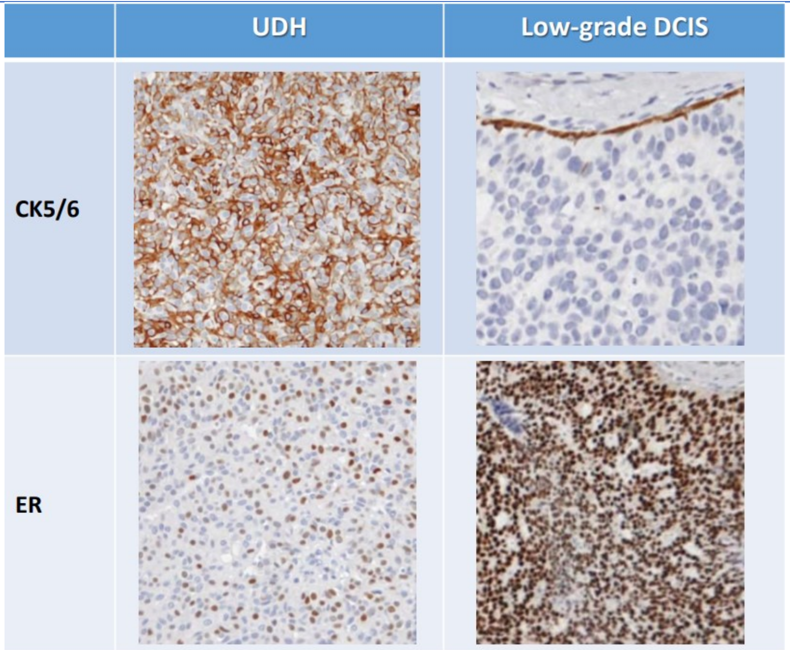


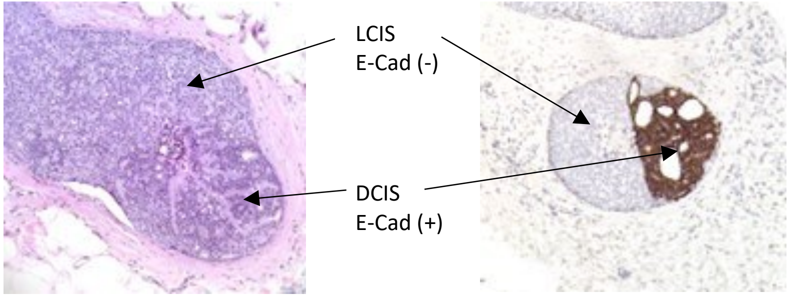
Figure: Comparison of multicentric versus multifocal DCIS created by Dr. Terrance Lynn, MD using BioRender.com


Multicentric
(>5 cm apart and in different quadrants)
Multifocal
(<5 cm apart and in same quadrant)

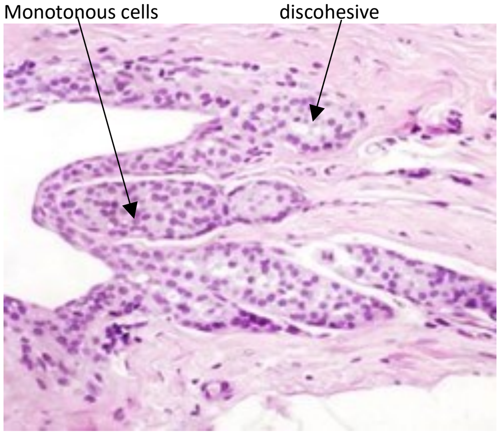

Multifocal DCIS
Necrosis
Adipose separating foci


UDH
Low-grade DCIS
CK5/6
ER

Collision of DCIS and LCIS, sorted out with E-cadherin (courtesy: Rhard Owings, MD)


LCIS
E-Cad (-)
DCIS
E-Cad (+)

Path Presenter


Monotonous cells
discohesive

ATYPICAL LOBULAR HYPERPLASIA (ALH)

MORPHOLOGY

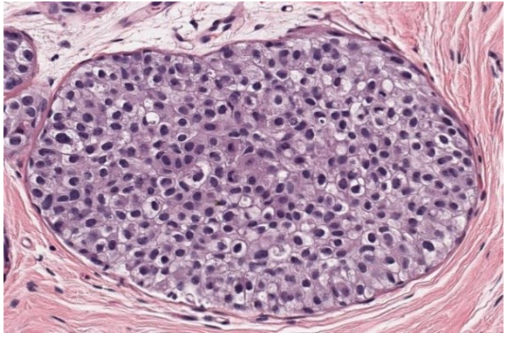
- A small proliferation of **discohesive**, **monomorphic** epithelial cells low to moderate grade nuclei
- It may have **pagetoid spread** through the ductal spaces

OTHER HIGH YIELD POINTS

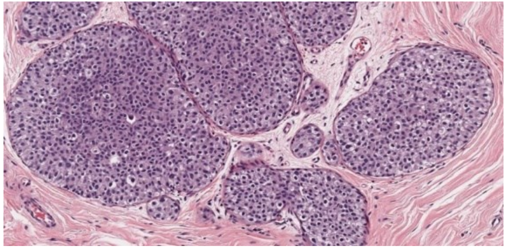
- Cytologically **similar to LCIS** but **limited to <1/2 of duct** involvement
- **Non-obligate precursor lesion**, common in premenopausal women
- Confers a **4 to 5-fold relative risk** for breast **cancer**
- The **lifetime risk of invasive carcinoma is about 15%,** and approximately **67%** of carcinoma **occurs in the ipsilateral breast** and 33% in the contralateral breast

Path Presenter

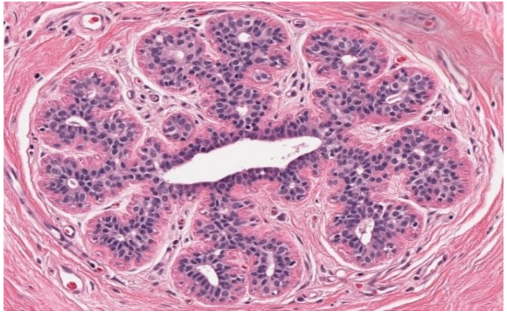
Monomorphic discohesive cells



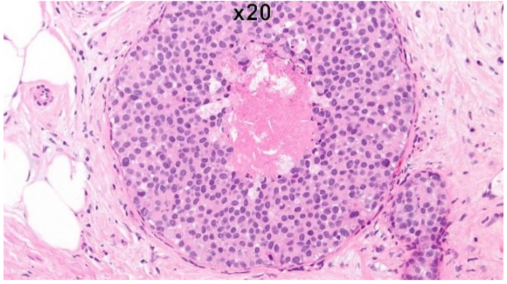
Florid LCIS expanding lobules



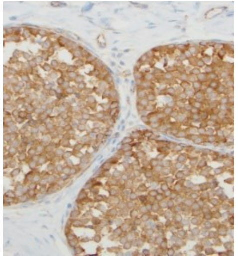
“Pagetoid” spread of LCIS in a duct



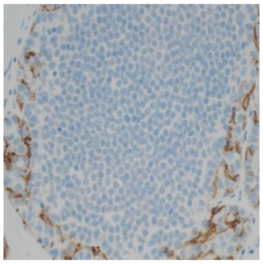
Pleomorphic LCIS (courtesy Mark Ong, MD)



Cytoplasmic p120



Loss of E-cadherin on IHC



Credits: @tissuepathology

LOBULAR CARCINOMA IN SITU

MORPHOLOGY

- **Classic LCIS**
  - **Discohesive**, **monomorphic** epithelial cells low to moderate grade nuclei that originate from the TDLU, **>50% of the acini are filled and expanded, often >8 cells thick**
  - It may have pagetoid spread through the duct space
- **Pleomorphic LCIS subtype:**
  - **Large epithelial cells** (>4x lymphocyte) with **marked** nuclear **pleomorphism** and may have **nucleoli** and **mitoses, intracytoplasmic vacuoles**
- **Florid LCIS Subtype:**
  - Classic LCIS cells but form a **confluent, mass-like lesion** with **little** or no **intervening stroma** between the distended TDLU (often ~50 cells in diameter)

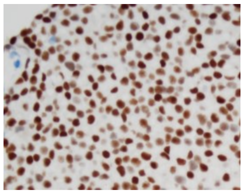
OTHER HIGH YIELD POINTS

- More than 50% of acini are filled/expanded by the neoplastic cells
- **Non-obligate precursor lesion** to invasive carcinoma that is most common in premenopausal women
- Confers an **8-10-fold relative risk for invasive breast cancer**
- The **lifetime risk** of invasive carcinoma is about **15%**, and approximately 67% of carcinoma occurs in the ipsilateral and 33% in the contralateral breast
- If **classic LCIS is present on core biopsy, there is no need to excise**; on surgical excision, no need to have clear margins
- Most often is **not associated with mammographic findings**
- If pleomorphic or florid LCIS, **excise with negative margins** due to their increased genomic instability and more aggressive behavior
- Increased incidence in women who are post-menopausal on HRT
- Possible treatment includes chemoprevention which reduces the subsequent risk of ER (+) cancer → **Tamoxifen reduces risk by ~50%**
- Special stains: Intracytoplasmic vacuole is **mucicarmine positive**

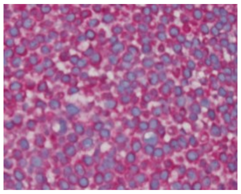
IHC STAIN	NORMAL EPITHELIUM	LOBULAR NEOPLASIA	DCIS
E-Cadherin	Membrane +	Negative	Membrane +
p120	Membrane +	Cytoplasmic	Membrane +
β-Catenin	Membrane +	Membrane stain lost	Membrane +

Feature	LCIS	DCIS
Loss of cohesion	Present	Absent
Intracytoplasmic vacuoles	More common	Less common
Pagetoid ductal involvement	More common	Less common
Microacini	Absent	Present
Polarization at duct periphery	Absent	Present

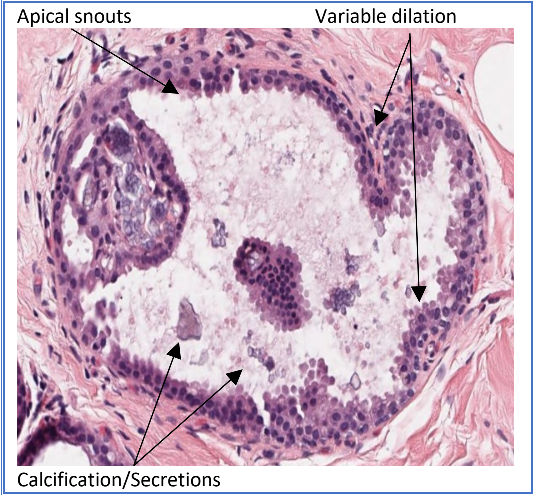
Path Presenter



Pleomorphic LCIS: ER



Pleomorphic LCIS: BNC-5



COLUMNAR CELL CHANGE

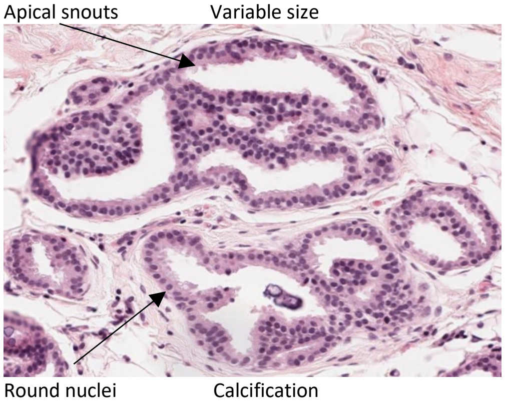
MORPHOLOGY

- Characterized by enlarged, **variably dilated acini** lined by **columnar epithelial cells** arranged **perpendicular to the basement membrane** and are 1-2 cells in thickness
- Cells are **uniform** and have **ovoid nuclei with regular chromatin** distribution, **inconspicuous nucleoli**, and have **apical cytoplasmic** blebs
- Apical snouts and **calcifications/secretions** are often present

OTHER HIGH YIELD POINTS

- The **earliest step in the low-grade** carcinoma **pathway**
- If > 2 cell layers thick → columnar cell hyperplasia
- **Infrequently associated with ADH, low-grade DCIS**, or invasive carcinoma
- **Risk of developing** a subsequent **carcinoma is negligible** (1.5x relative risk)
- IHC: Strongly ER (+), CK8/18 (+); CK5/6 (-)

Path Presenter



Path Presenter

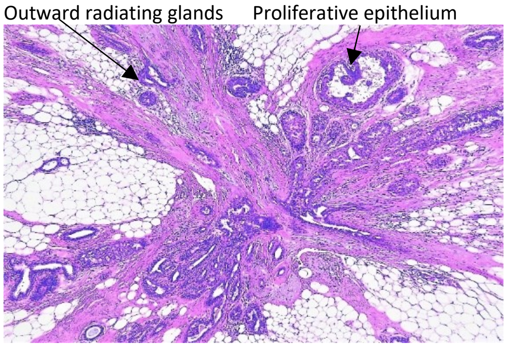
FLAT EPITHELIAL ATYPIA

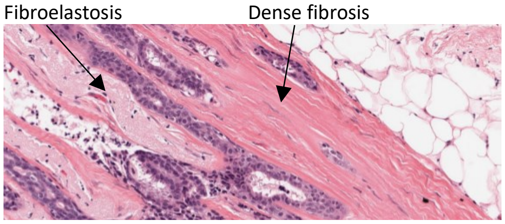
MORPHOLOGY

- **Monomorphic cuboidal to columnar cells** with nuclei that are round with minimal nuclear contour irregularities, and are **polarized**
- It can be arranged in **complex architecture**
- May have **calcifications**, secretions, and apical snouts

OTHER HIGH YIELD POINTS

- The **relative risk for cancer is 1.5-fold**, and the **lifetime risk of 5%**
- If FEA is found in the targeted lesion, less than 5% of cases will have associated cancer but is an indication for excision to exclude worse lesion in close proximity
- **Same cells as in ADH/DCIS**
- If complex architecture present it is not FEA but rather ADH or DCIS
- IHC: **ER will be strongly and diffusely positive** throughout the lesion
- Molecular: Often has loss of 16q





RADIAL SCLEROSING LESION (RADIAL SCAR)

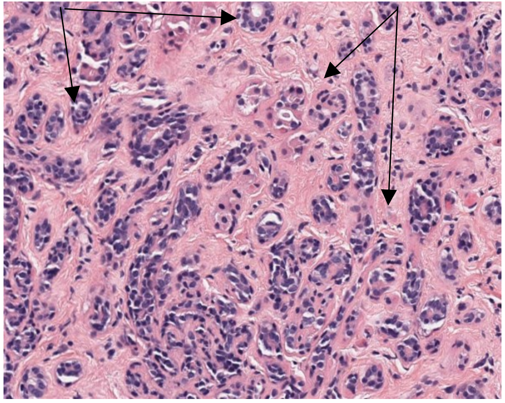
MORPHOLOGY

- **Stellate**, dense **fibroelastosis** with **entrapped glandular structures** in a **radiating outward** configuration
- **Two cell layers** maintained throughout lesion
- It may have associated proliferative epithelial lesions (e.g., UDH/ADH/DCIS)

OTHER HIGH YIELD POINTS

- **Radiographically** is a **spiculated lesion** and may have associated calcifications
- **Radial scar** → Smaller with a stellate configuration
- **Complex sclerosing lesion** → Larger and more disorganized than radial scar
- Approximately **2/3rd will have a *PIK3CA* mutation**
- Myoepithelial IHC helps exclude invasive carcinoma
- Confers **approximately a 1.5-to-2-fold increase in the risk of invasive carcinoma**, and the **lifetime risk of carcinoma is 5-7%** in either breast regardless of which had the radial sclerosing lesion

Path Presenter


Acini & Tubules
Compressing fibrosis
Myoepithelial cells

SCLEROSING ADENOSIS

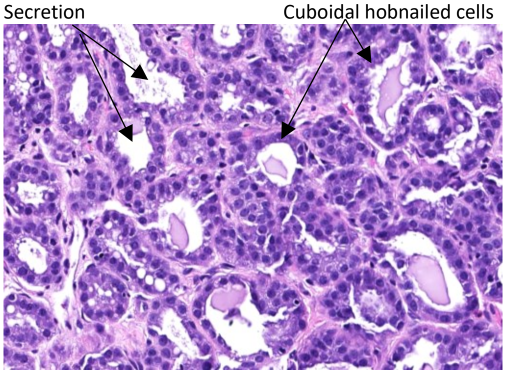
MORPHOLOGY

- **Lobulocentric proliferation** of **acini and tubules** accompanied by **compressing fibrosis**
- **Epithelial cells** are often **cuboidal, small,** and cytologically **bland**
- **Myoepithelial cells** have spindled, hyperchromatic nuclei and inconspicuous to prominent clear cytoplasm
- **Microcalcifications** are common

OTHER HIGH YIELD POINTS

- Can be involved by epithelial proliferations (UDH, etc.)
- **Easily confused** with **carcinoma**
- Useful IHC stains: **Myoepithelial markers** (p63, CK5/6). S100 (-); BNC-5 polyclonal cytokeratin expression and retained myoepithelial cells

Path Presenter


Secretion
Cuboidal hobnailed cells
Densely pack glands

LACTATING ADENOMA

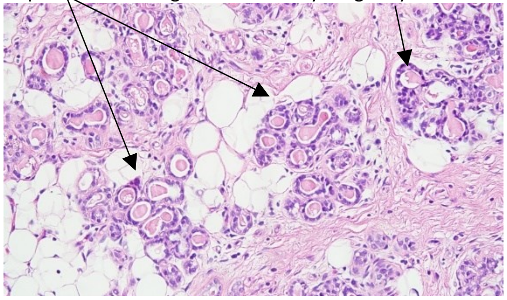
MORPHOLOGY

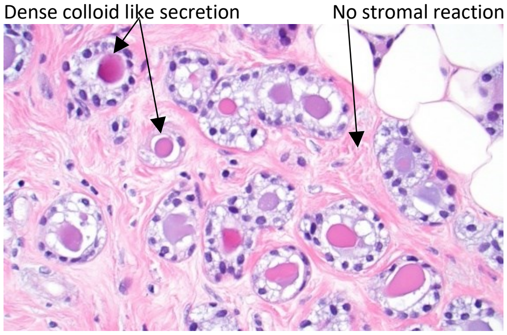
- **Well-circumscribed** proliferation of closely packed **hyperplastic secretory lobules** separated by **delicate connective tissue**
- **Cuboidal to hobnailed** epithelial cells are **bland** with **vacuolated to granular cytoplasm** and small, uniform, pinpoint nucleoli

OTHER HIGH YIELD POINTS

- Benign nodules are usually **diagnosed during pregnancy/breastfeeding**
- **Spontaneously regresses** after completion of lactation
- **No** known **progression to carcinoma**
- Can be **present anywhere along the mammary line**

Path Presenter


Haphazard tubular glands
Cytologically bland cells


Dense colloid like secretion
No stromal reaction

Picture credits: Reza Eshraghi, MD and Lorand Kis, MD

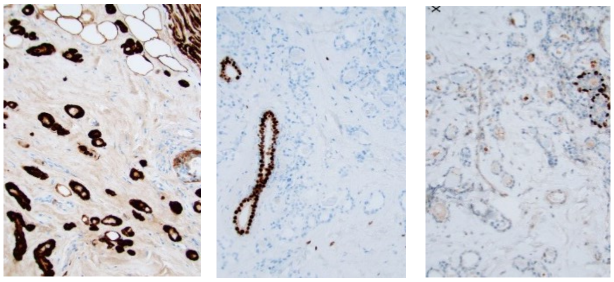
MICROGLANDULAR ADENOSIS

MORPHOLOGY

- A **haphazard proliferation** of small, round, uniform, **tubular glands** composed of a **single layer of epithelium** (without associated myoepithelial cells) that have **bland nuclei** and **amphophilic cytoplasm**
- Luminal spaces are open and often have **eosinophilic colloid-like secretion**

OTHER HIGH YIELD POINTS

- About **25% of cases** are **associated** with **invasive carcinoma**
- Hypothesized to be **non-obligate precursor of basal-type** breast **cancer**
- IHC: **Cytokeratin** (+), s100 (+); (-)for ER, PR, HER2, and **myoepithelial markers**
- Molecular findings include **copy number alterations**, ***TP53*** mutations, ***PIK3CA***, and ***BRCA1*** mutations


S100 ER P63

Path Presenter

TUBULAR ADENOMA

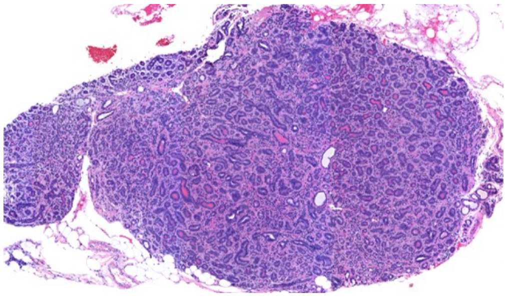
MORPHOLOGY

- Well-circumscribed, sharply demarcated, and dense proliferation of closely approximated round to oval tubular structures with little background stroma
- Glands have the usual two layers: Epithelium and myoepithelium

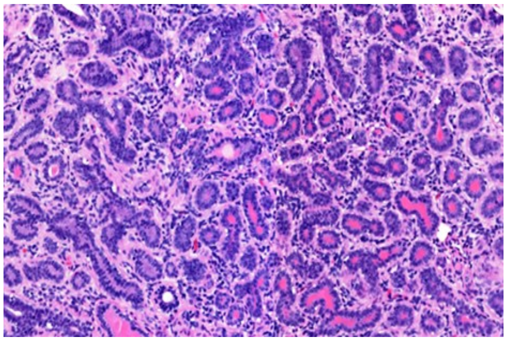
OTHER HIGH YIELD POINTS

- Uncommon, usually in younger women in the upper outer quadrant
- Lack a *MED12* mutation (seen in fibroepithelial lesions)

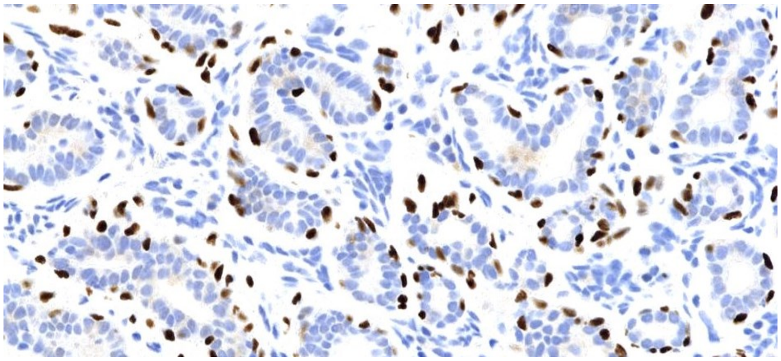
Well circumscribed



Dense tubules with little stroma



Picture credits: Reza Eshraghi, MD



Path Presenter

P63 immunostain

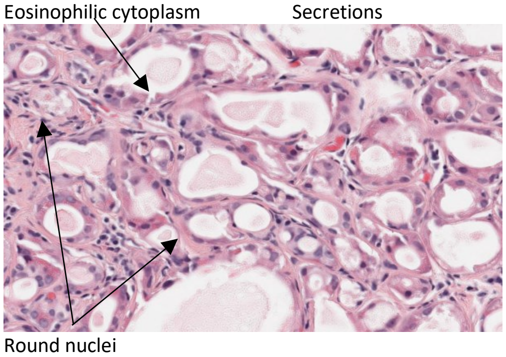
APOCRINE ADENOSIS

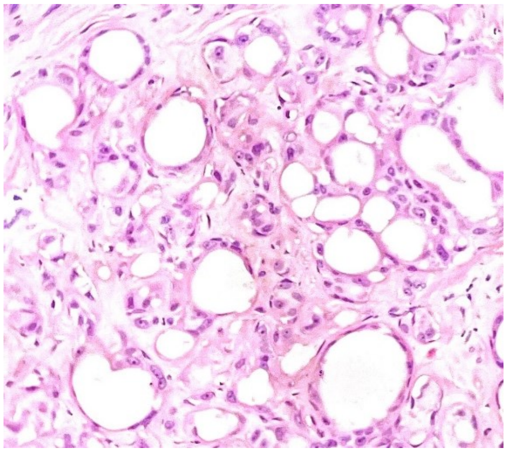
MORPHOLOGY

- **Lobulocentric proliferation** of benign **glandular** structures composed of epithelial cells with **abundant granular cytoplasm**
- Apocrine cells have **round nuclei** and **prominent nucleoli**

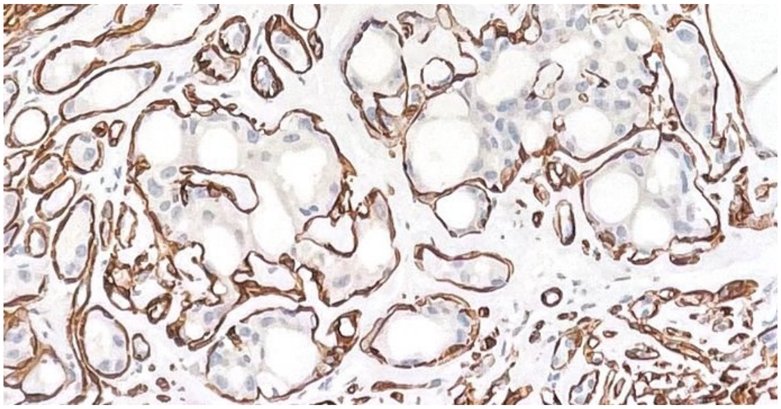
OTHER HIGH YIELD POINTS

- Think **apocrine metaplasia + sclerosing adenosis** = **apocrine adenosis**
- If significant cytologic **atypia → Atypical Apocrine Adenosis**
- If **complex architecture** (cribriform, marked pleomorphism) → **Apocrine DCIS**
- IHC : (+) myoepithelial cells; epithelial cells are ER(-) but AR and GCDFP-15(+)





Courtesy: Amal Asar, FRCpath.



Path Presenter

SMM immunostain

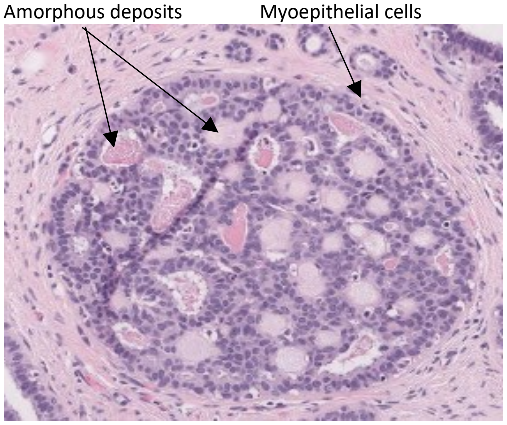
COLLAGENOUS SPHERULOSIS

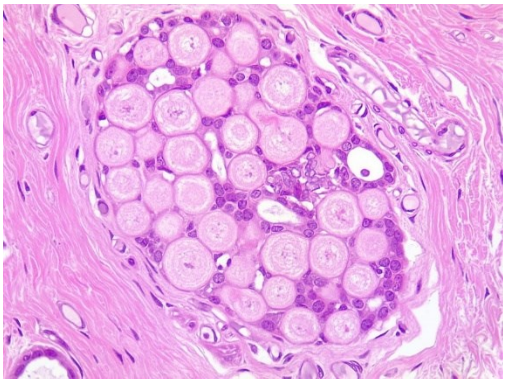
MORPHOLOGY

- **Intraductal deposits** of **basement membrane** which are **amorphous** and **eosinophilic**, acellular, eosinophilic, or fibro papillary spherules
- **Myoepithelial cells surround the lumina** and are often compressed and spindle-shaped
- May or may not have calcifications

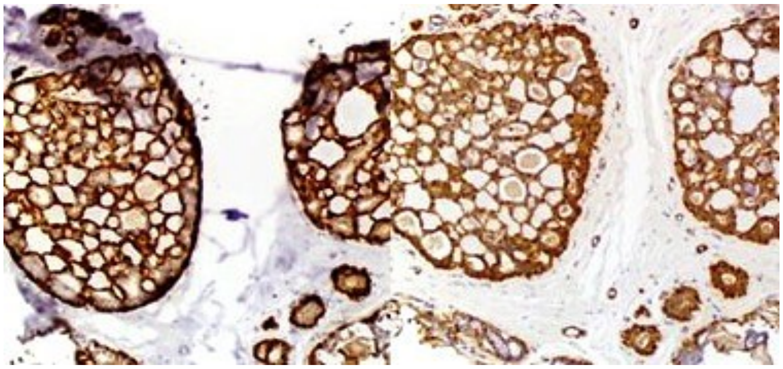
OTHER HIGH YIELD POINTS

- **Commonly seen** with **papilloma**, **UDH**, or **sclerosing lesions**
- Easily **confused for DCIS** or **adenoid cystic carcinoma**
- The matrix material is **PAS-positive** and **Alcian Blue positive**





Courtesy: Ari Abdullah, MD



Calponin and SMA immunostains Courtesy: Mohamed Kahila, MD

[Path Presenter]

GYNECOMASTIA

MORPHOLOGY

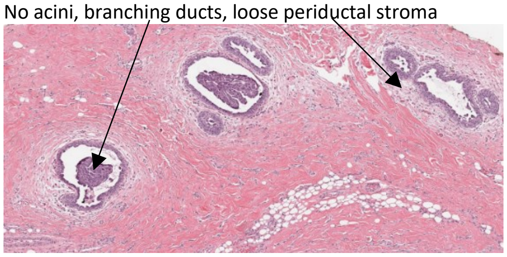
- Contains **fibrous stroma** and **branching ducts**, and terminal ductules, but extremely few (if any) acini
- **Early stage** → Loose **periductal stroma** and **mixed chronic inflammatory infiltrate**, extensive epithelial **hyperplasia**, **tapering tufts** (**pyramid-shaped micropapillae)**
- **Late stage→ Fibrosis** and **hyalinization** of periductal stroma and **epithelial atrophy**
- May have **pseudoangiomatous hyperplasia (PASH)**
- Absence of lobules

OTHER HIGH YIELD POINTS

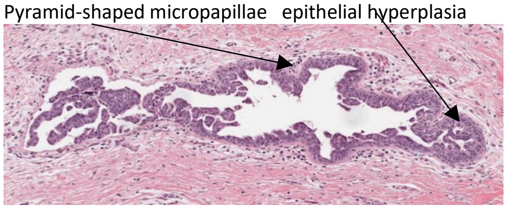
- **Benign lesion** of the male breast and is **often bilateral**
- Caused by **androgen/estrogen imbalance** and is **physiologic in children** but often **pathologic in adults**
- Can be seen during **puberty**, taking **dopaminergic medications**, hormone therapy, **Klinefelter syndrome**, **cirrhosis**, or **obesity**
- **Not associated with** any risk of **cancer**

[Path Presenter]

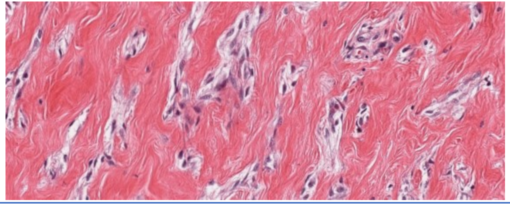
No acini, branching ducts, loose periductal stroma



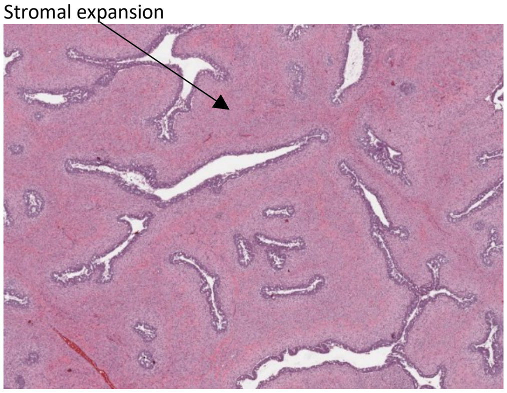
Pyramid-shaped micropapillae epithelial hyperplasia

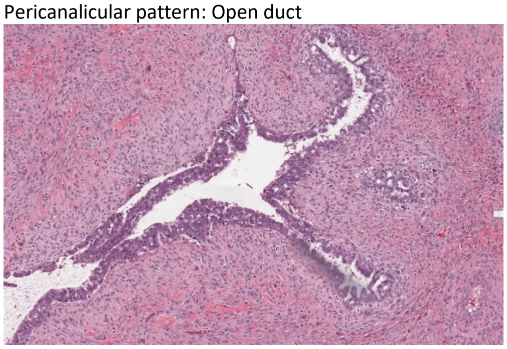


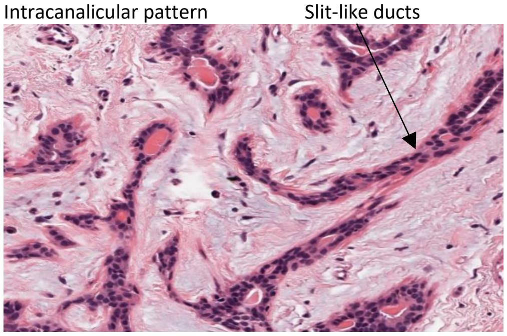
Pseudoangiomatous stromal hyperplasia



FIBROEPITHELIAL LESIONS


Stromal expansion


Pericanalicular pattern: Open duct


Intracanalicular pattern
Slit-like ducts

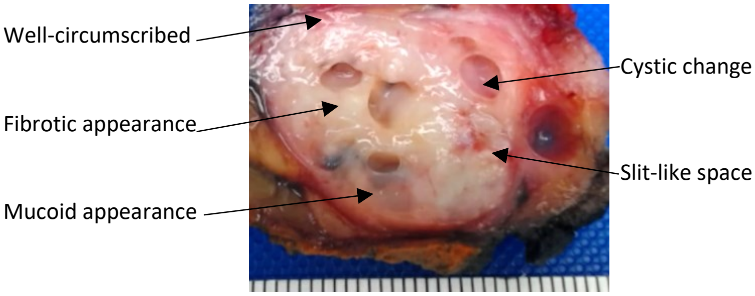
FIBROADENOMA

MORPHOLOGY

- **Circumscribed, benign neoplasm** of the Terminal Duct Lobular Unit (TDLU) with a **biphasic proliferation** of **epithelial** and **stromal** cells
- **Intracanalicular pattern:**
  - ➢ Expansion of stroma compresses ducts into slit-like spaces
- **Pericanalicular pattern:**
  - ➢ Stroma grows around open ducts
- **Absence of stromal overgrowth**, cytologic **atypia**, significant **mitotic activity**, or **well-developed fronds**

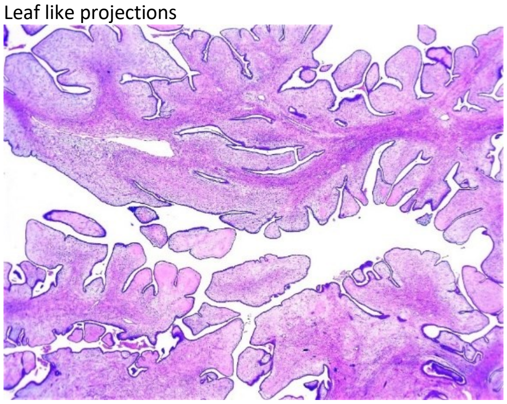
OTHER HIGH YIELD POINTS

- The **most common benign** solid breast **mass in young women**
- Most are **slow growing** and **painless**, and **unilateral**
- Most fibroadenomas **do not recur** after complete surgical excision
- **Juvenile Fibroadenoma:** Usually large and have rapid growth and are predominantly have pericanalicular growth
- Immunohistochemistry:
  - ➢ **Stromal cells:** Positive for CD34, PR, ER-beta, Beta catenin (nuclear)
  - ➢ **Epithelial cells:** CK7, CKAE1/AE3, ER-alpha
- **About 60-65% will have a *MED12* mutation** (stromal cells) but the **myxoid fibroadenoma will lack** this mutation


Well-circumscribed
Fibrotic appearance
Mucoid appearance
Cystic change
Slit-like space

Path Presenter

PHYLLODES TUMOR

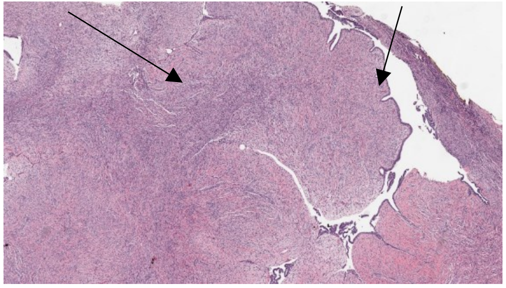

Leaf like projections

MORPHOLOGY

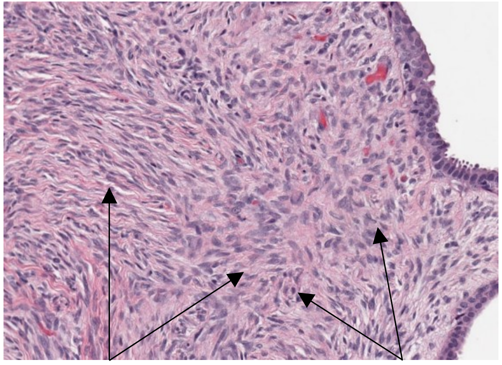
- **Biphasic tumor** composed of spindled stromal cells and benign epithelial cells
- **Stromal cellularity is variable** and ranges from paucicellular to hypercellular
- Prominent intracanalicular growth pattern
- Exaggerated intracanalicular growth→ **"Leaf-like" projections** into variably dilated lumina

OTHER HIGH YIELD POINTS

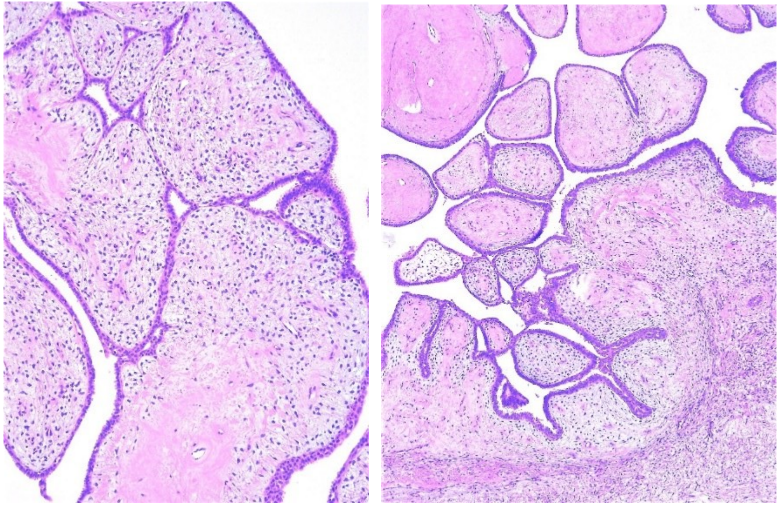
- **Increased incidence** in patients **with Li-Fraumeni syndrome**
- Presents as a **palpable painless breast mass**
- Can have **heterologous elements that are malignant**
- **Molecular**: MED12 and RARA mutations seen in benign phyllodes; TERT promoter, ERBB4, TP53, EGFR, PIK3CA, **RB1 seen in borderline and malignant** phyllodes tumors


Stromal overgrowth
Projection

Benign Phyllodes tumor


Minimal atypia
Cellular stroma

- Treatment: wide local excision
- **Singapore nomogram** used for predicting **recurrence**
  - **Atypia** in stroma
  - **Mitoses**
  - **Overgrowth**
  - Surgical **margin**



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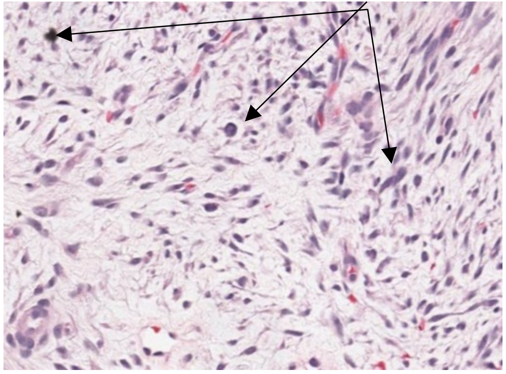
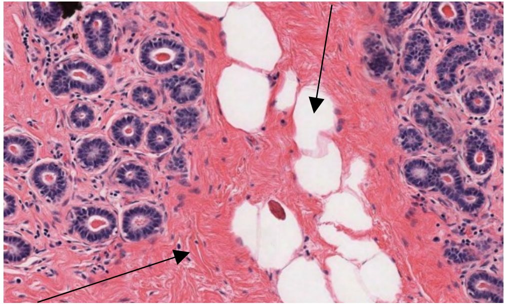
Malignant Phyllodes tumor


Stromal atypia

CLASSIFICATION OF PHYLLODES TUMORS			
	BENIGN	**BORDERLINE**	**MALIGNANT**
Stromal Atypia	Mild	Moderate	Marked
Stromal Cellularity	Minimal to mild	Moderate	Marked and diffuse
Stromal Overgrowth	Not present	Not present or very focal	Present
Mitoses	<5/10 HPF	5-9/10HPF	≥10/10 HPF
Border	Well defined	Well defined	Infiltrative
Malignant Heterologous elements	Not present	Not present	If present, upgrades to malignant


Ducts
Adipose tissue
Fibrous stroma

HAMARTOMA

MORPHOLOGY

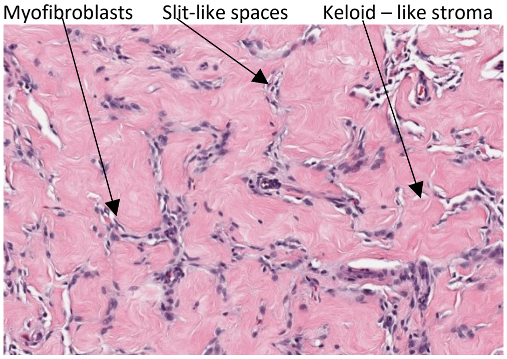
- Composed of **normal ducts, lobules, fibrous tissue, and adipose tissue** in varying proportions (normal components)
- **Well circumscribed**

OTHER HIGH YIELD POINTS

- Sometimes called “adenolipoma”
- Clinical presentation is a **painless breast mass**
- Requires clinical and/or imaging correlation to distinguish from normal breast

Path Presenter

SPINDLE CELL LESIONS



PSEUDOANGIOMATOUS STROMAL HYPERPLASIA (PASH)

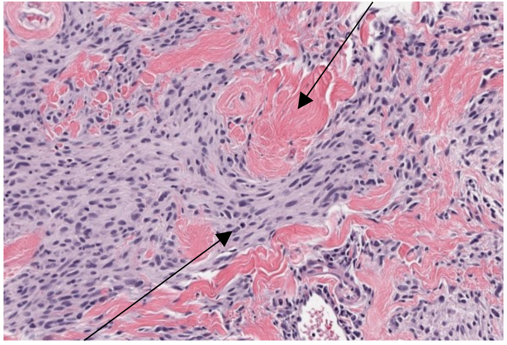
MORPHOLOGY

- **Keloid-like stroma** with **complex anastomotic spaces** that are often empty and have **peripherally placed myofibroblasts**

OTHER HIGH YIELD POINTS

- Benign breast lesion with **aberrant stromal response** to hormone
- Presents as an **incidental mass-forming lesion**
- IHC: Spindle cells positive for CD34, PR, and AR; negative for cytokeratin and CD31

Path Presenter



MYOFIBROBLASTOMA

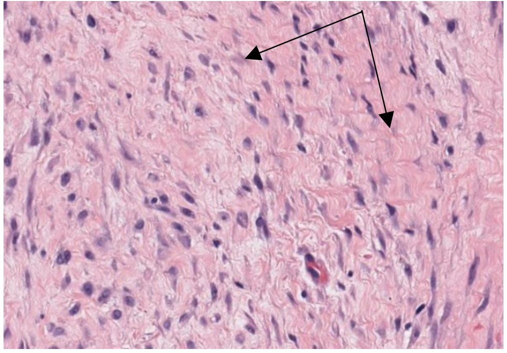
MORPHOLOGY

- **Bland**, **spindled cells** composed of **fibroblasts** and **myofibroblasts** that are arranged in short, **haphazardly intersecting fascicles**
- Interspersed **thick collagen bundles**, **minimal** mitoses, and **atypia**

OTHER HIGH YIELD POINTS

- Often presents as a **slow-growing, painless mass**
- **Well-circumscribed** and **unencapsulated**
- IHC: Shows **loss of RB1**; spindle cells are positive for desmin, CD34, ER, PR, AR
- FISH: 13q14 deletions
- **Treatment**: Cured by **local excision**

Path Presenter



DESMOID FIBROMATOSIS

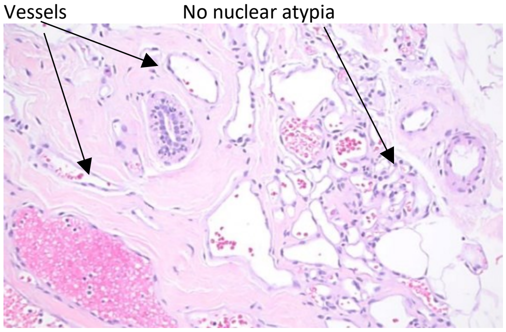
MORPHOLOGY

- **Broad**, **sweeping fascicles** of uniform **spindled cells** with small, pale nuclei with pinpoint nucleoli
- **Moderate amounts** of **collagen** and may be slightly myxoid
- **Microhemorrhages** and scattered **chronic inflammation** are common

OTHER HIGH YIELD POINTS

- Benign (**never metastasize**), but **infiltrative** with a strong **tendency to recur** (>25%), microscopic **margins do NOT predict recurrence**
- Often have infiltrative growth into surrounding structures
- IHC: Nuclear β-catenin+, Actin (+/-)
- Molecular: FAP (if syndromic); CTNNB1

Path Presenter



HEMANGIOMA

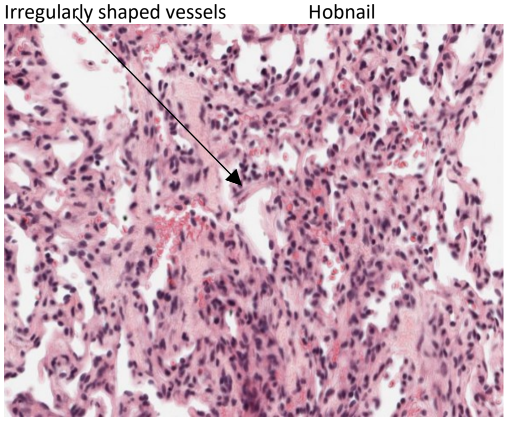
MORPHOLOGY

- Benign **proliferation of mature** blood **vessels without** nuclear **atypia** (hyperchromasia or pleomorphism), **mitoses**, **or multi-layering**

OTHER HIGH YIELD POINTS

- Usually found incidentally and most common in middle-aged females
- If superficial, it can show red-purple coloring on the skin
- IHC: **Positive for CD31, CD34, and ERG**

Path Presenter


Irregularly shaped vessels
Hobnail

ATYPICAL VASCULAR LESION

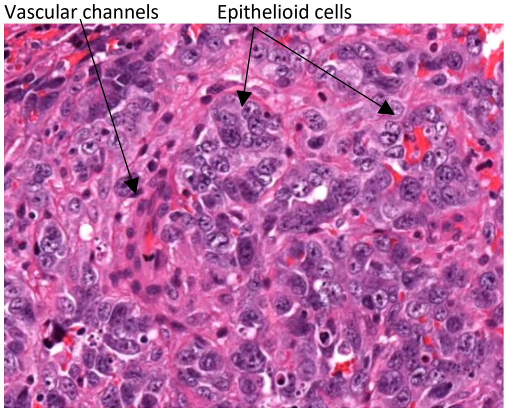
MORPHOLOGY

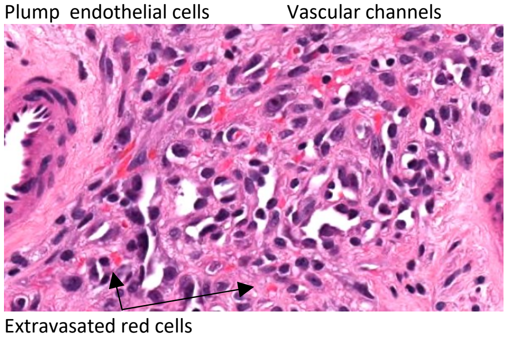
- **Irregularly shaped**, thin-walled **vessels** with **branching** and anastomotic growth
- Lumen is lined by a **single layer of endothelial cells** with some **hobnail** and **hyperchromatic** features
- **No** endothelial cell **multilayering** or true cytologic **atypia**

OTHER HIGH YIELD POINTS

- **Benign** condition, often occurs in irradiated skin of breast
- **Multiple lesions** may be present
- If superficial, it can show red-purple coloring on the skin
- IHC: positive for CD31, CD34, ERG; **no MYC overexpression/amplification**

Path Presenter


Vascular channels
Epithelioid cells


Plump endothelial cells
Vascular channels
Extravasated red cells

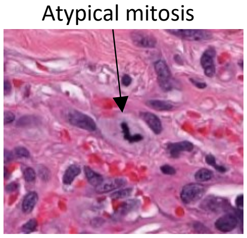
ANGIOSARCOMA

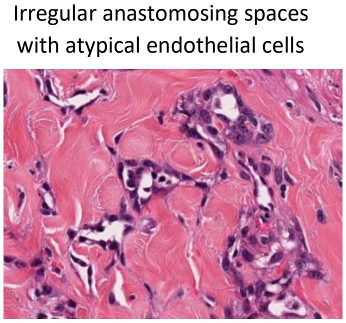
MORPHOLOGY

- **Spindled** to **plump epithelioid cells** line vascular channels
- Vascular spaces are pinpoint or dilated and have **exuberant anastomosis**
- The **nuclei** of these cells often contain **a "bullet" shaped nucleolus**
- May have **hemosiderin**, **necrosis**, **atypical mitoses**, and **high-grade foci**

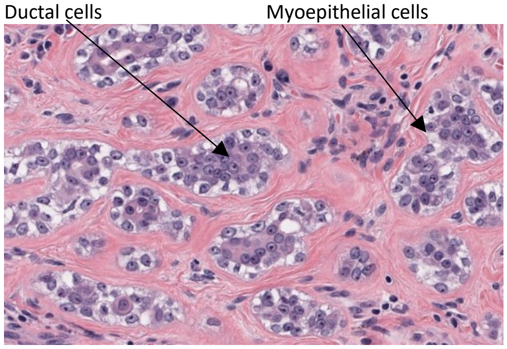
OTHER HIGH YIELD POINTS

- Usually found **incidentally** and most common in **middle-aged females**
- If superficial, it can show **red-purple coloring on the skin**
- **Post-radiation angiosarcoma** occurs approximately **5 years post-radiation**
- IHC: **Positive** for CD31, CD34, **ERG**, **high ki-67** proliferation index; **MYC positive** in **post-radiation** angiosarcoma


Atypical mitosis


Irregular anastomosing spaces with atypical endothelial cells

Path Presenter


Ductal cells
Myoepithelial cells

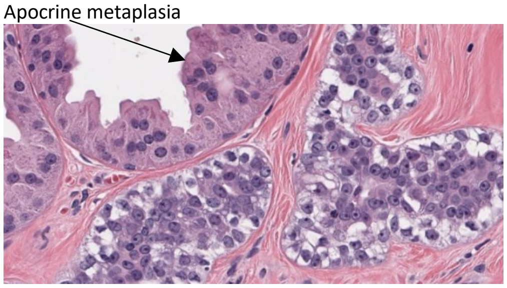
ADENOMYOEPITHELIOMA

MORPHOLOGY

- **Biphasic proliferation** of **inner ductal** cells and **outer myoepithelial** cells
- May have **various patterns**, but can be **papillary** or **tubular** with prominent myoepithelial cells with clear cytoplasm or more spindled
- **Well circumscribed** and can be encapsulated
- May have **sebaceous, squamous, or apocrine metaplasia**
- May have **mild to moderate** nuclear **atypia** but **no mitosis or necrosis**

OTHER HIGH YIELD POINTS

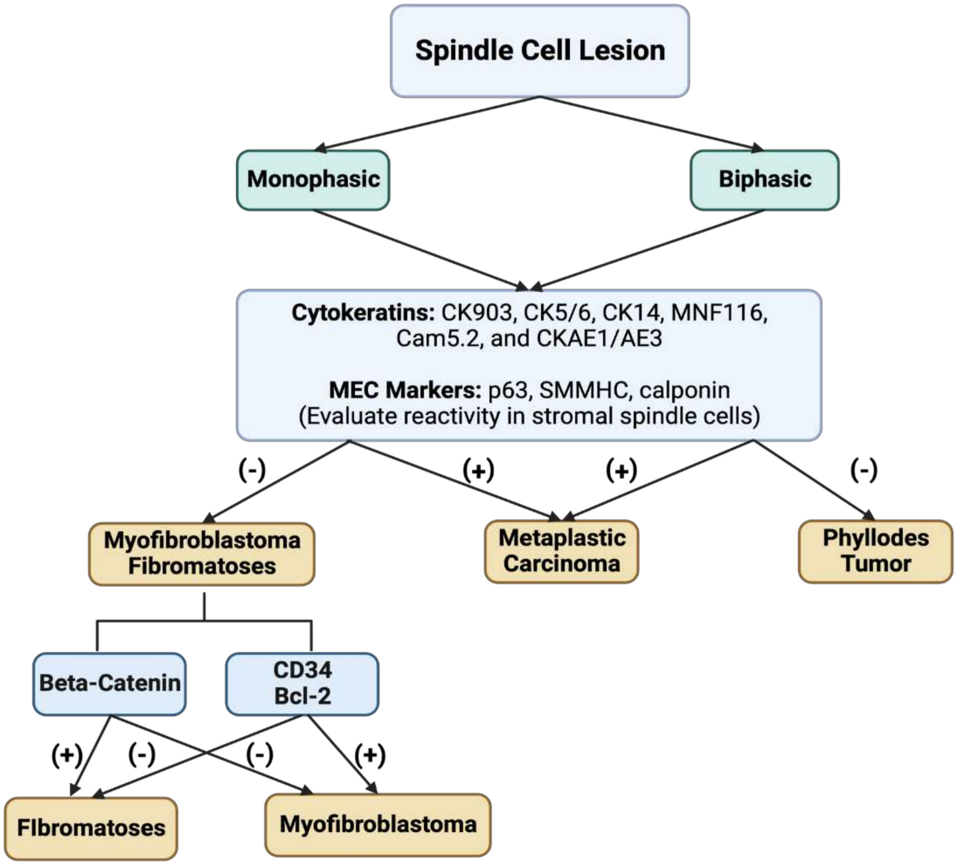
- Usually found **in older females** with a **palpable breast mass**
- **Peripheral location** more often seen than central or areolar


Apocrine metaplasia

- **Can de-differentiate** into **carcinoma (any type)** or **malignant transformation**
  - High mitotic count, infiltrative borders, severe atypia in either myoepithelial or ductal cells
- Immunohistochemistry:
  - **Epithelial component:** CKAE1/AE3, CK7, EMA, Cam5.2, ER
  - **Myoepithelial component:** p63, S100, SMMHC, SMA
- Molecular: Frequent mutations in PIC3CA or AKT1 (in ER positive) and HRAS Q61R (in ER negative)

Path Presenter

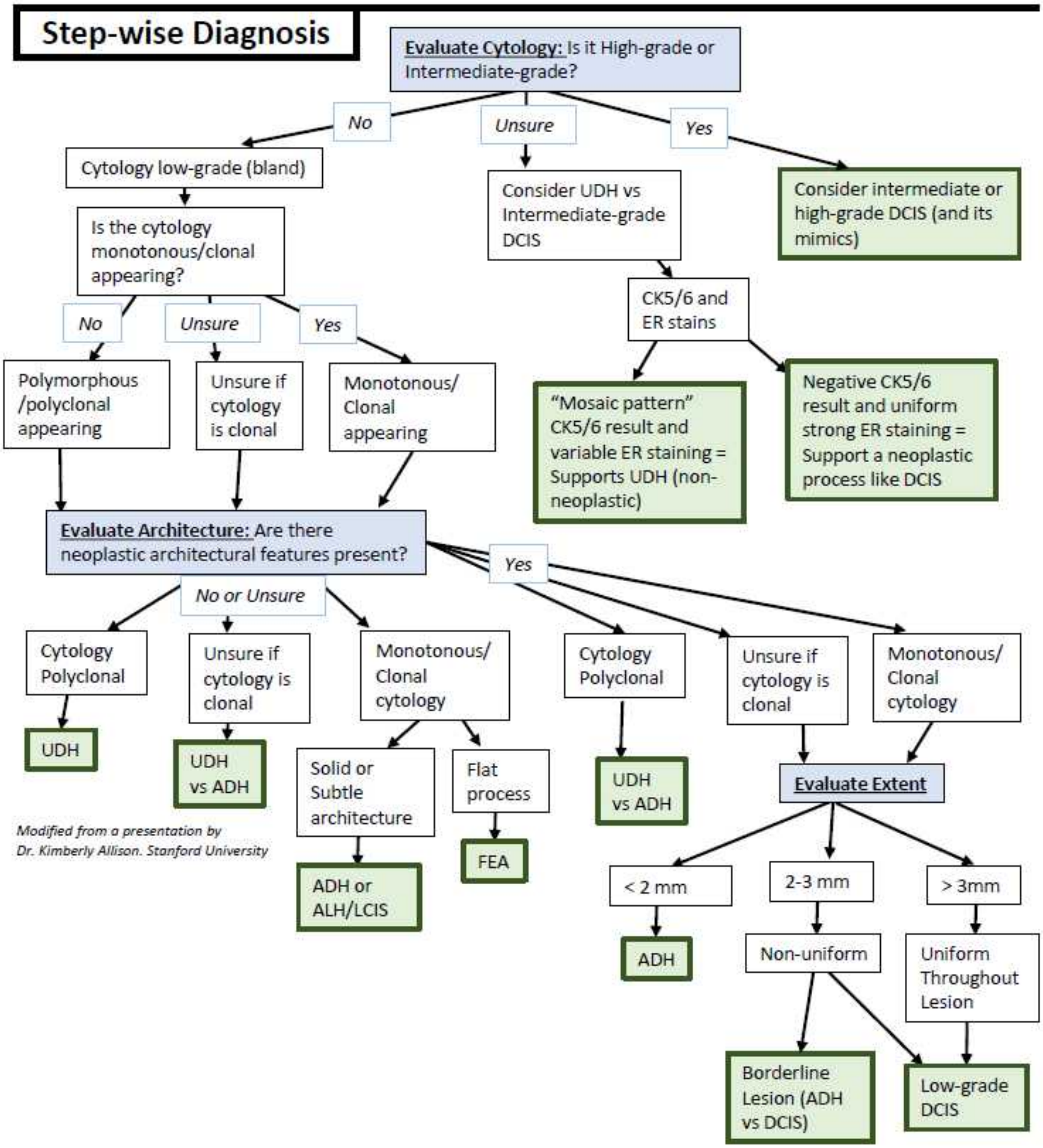
BREAST SPINDLE CELL NEOPLASM ALGORITHM FOR SELECTING IHC PANEL


Spindle Cell Lesion
Monophasic
Biphasic
Cytokeratins: CK903, CK5/6, CK14, MNF116, Cam5.2, and CKAE1/AE3
MEC Markers: p63, SMMHC, calponin
(Evaluate reactivity in stromal spindle cells)
(-)
(+)
(+)
(-)
Myofibroblastoma Fibromatoses
Metaplastic Carcinoma
Phyllodes Tumor
Beta-Catenin
CD34
Bcl-2
(+)
(-)
(-)
(+)
FIbromatoses
Myofibroblastoma

Tip: For spindle cell lesions, always consider **metaplastic carcinoma** and/or **stromal overgrowth in a Phyllodes Tumor.** Sample the lesion well, looking for an epithelial component and stain it with multiple epithelial markers. Given the limitations of sampling, be particularly careful (and perhaps more descriptive) on core biopsies! **Always** be very weary diagnosing a primary sarcoma in the breast! MEC: Myoepithelial component.

Created by Dr. Terrance Lynn using BioRender.com. *Adapted from Liu. H. Application of immunohistochemistry in breast pathology: a review and update. Arch Pathol Lab Med. 2014 Dec;138(12):1629-42.*

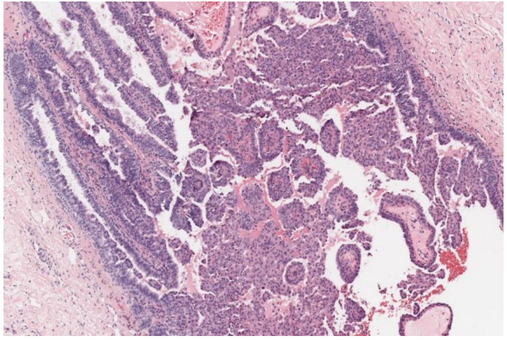
STEP-WISE ALGORITHM OF BENIGN AND INSITU BREAST NEOPLASMS

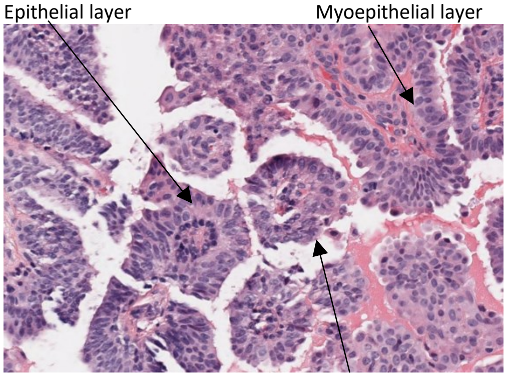

Step-wise Diagnosis
Evaluate Cytology: Is it High-grade or Intermediate-grade?
No
Unsure
Yes
Cytology low-grade (bland)
Consider UDH vs Intermediate-grade DCIS
Consider intermediate or high-grade DCIS (and its mimics)
Is the cytology monotonous/clonal appearing?
CK5/6 and ER stains
No
Unsure
Yes
Polymorphous /polyclonal appearing
Unsure if cytology is clonal
Monotonous/ Clonal appearing
"Mosaic pattern" CK5/6 result and variable ER staining = Supports UDH (non-neoplastic)
Negative CK5/6 result and uniform strong ER staining = Support a neoplastic process like DCIS
Evaluate Architecture: Are there neoplastic architectural features present?
No or Unsure
Yes
Cytology Polyclonal
Unsure if cytology is clonal
Monotonous/ Clonal cytology
Cytology Polyclonal
Unsure if cytology is clonal
Monotonous/ Clonal cytology
UDH
UDH vs ADH
Solid or Subtle architecture
Flat process
UDH vs ADH
Evaluate Extent
Modified from a presentation by Dr. Kimberly Allison. Stanford University
ADH or ALH/LCIS
FEA
< 2 mm
2-3 mm
> 3mm
ADH
Non-uniform
Uniform Throughout Lesion
Borderline Lesion (ADH vs DCIS)
Low-grade DCIS

Modified from a presentation by Dr. Kimberly Allison at Stanford University.

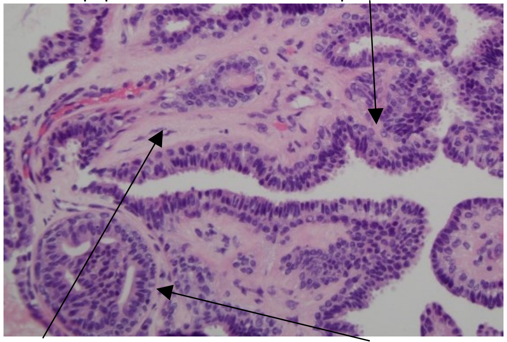
PAPILLARY LESIONS

Intraductal papillary proliferation

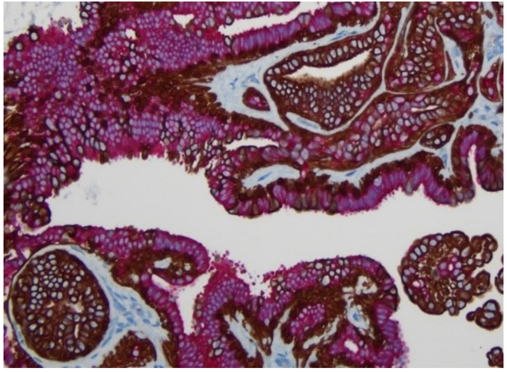




Sclerotic papilloma



BNC-5 stain showing retained myoepithelial cells and polyclonal keratin expression



INTRADUCTAL PAPILLOMA

MORPHOLOGY

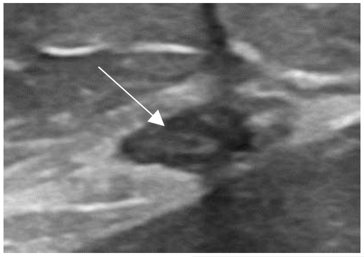
- **Benign intraductal proliferation** composed of **papillary projections** with fibrovascular cores, covered by **epithelial** and **myoepithelial** cell **layers**
- May have **superimposed proliferative changes** such as UDH, apocrine metaplasia, sclerosing adenosis, or duct ectasia
- Can be **sclerotic** or undergo **infarction**, especially **after biopsy**

OTHER HIGH YIELD POINTS

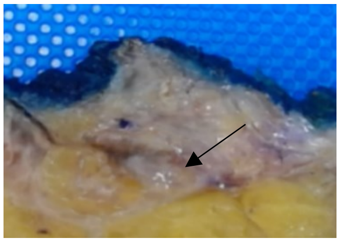
- Can be broken into **two categories** based on their location within the ducts
- **Small duct papilloma (SDP):**
  - **Peripherally located** within TDLU and **usually** there are **multiple**
  - The relative **risk of carcinoma** is approximately a **3-fold increase**
  - Usually is mass that is < 1cm and not readily palpable on exam
- **Large duct papilloma:**
  - **Centrally located within lactiferous duct and usually solitary**
  - The relative **risk of carcinoma** is approximately a **2-fold increase**
  - Standard treatment is to **surgically excise**
- Often present with **serosanguinous nipple discharge**
- **Risk factors for carcinoma** on excision include: **>1 cm** in size, **old age**, and palpable **mass** or **discharge**
- **Gross examination**: Usually tan-pink bosselated or papillary nodule that is protruding into dilated duct space; may have serosanguinous fluid
- Immunohistochemistry:
  - **Myoepithelial markers:** p63(+), SMA(+)
  - **Epithelial markers:** CK5/6 (+ heterogenous), ER (+ heterogenous), and a **BNC-5** showing a **polyclonal keratin** expression
- **Molecular: PIK3CA** (about **40%**), **AKT1** (about **30%**) **activating point mutations** and about **50% of all papillomas** will **have** either **mutation**

Path Presenter

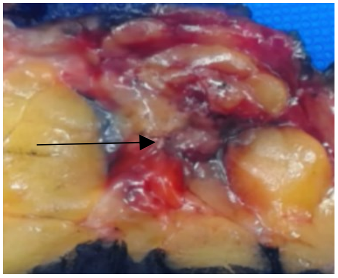
Ultrasound of IDP

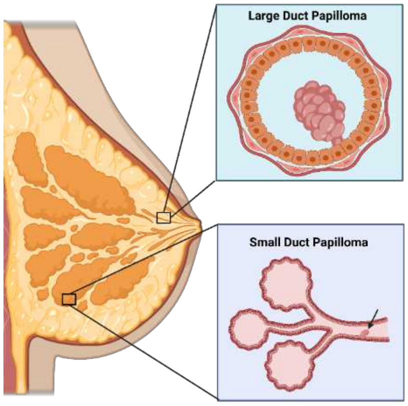


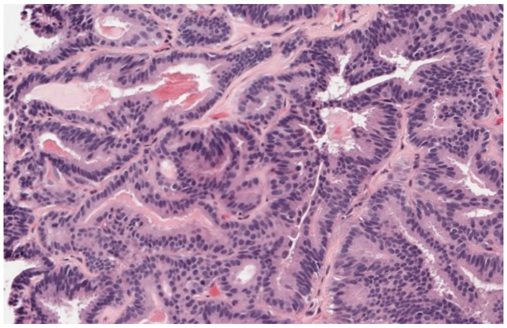
Section showing Sclerotic IDP

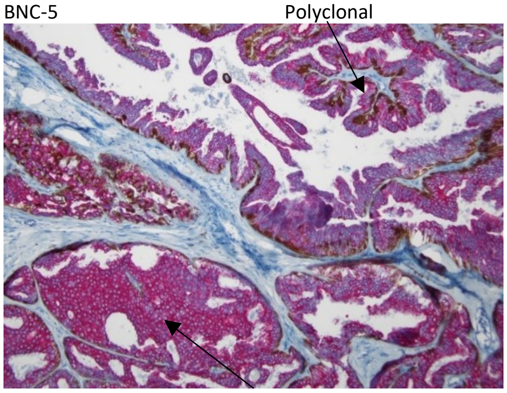


Section of large duct papilloma









PAPILLOMA INVOLVED BY DUCT CARCINOMA IN SITU

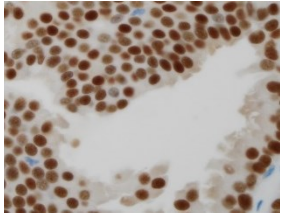
MORPHOLOGY

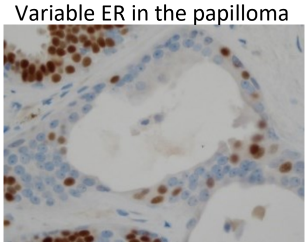
- **Foci of DCIS (or ADH**) superimposed **in** an intraductal **papilloma**
- Focal population of **monotonous cells** with **cytologic** and **architectural** atypia showing low-grade neoplastic ductal process
- **Monotonous cells** will demonstrate **polarization** around lumina

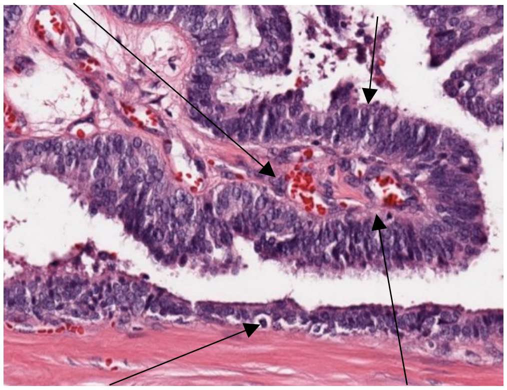
OTHER HIGH YIELD POINTS

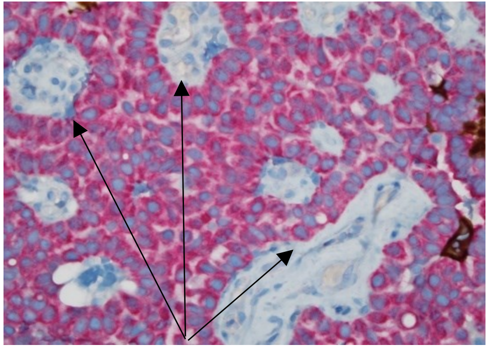
- **Size criteria** for ADH versus DCIS is utilized **except for** lesions in which there is **intermediate** or **high-grade cytology** as these **automatically** are **DCIS**
- For low-grade lesions:
  - **Lesions <3 mm** are classified as **atypical duct hyperplasia** (**ADH**)
  - **Lesions ≥ 3 mm** are best classified as **Ductal carcinoma in situ (DCIS)**
- Immunohistochemistry:
  - **DCIS component:** BNC-5 will show clonal cytokeratin expression and **ER** will be **diffuse and strong**
  - **Papilloma component:** BNC-5 will show polyclonal cytokeratin expression and ER will be **heterogenous**

Path Presenter


Diffuse ER in DCIS component


Variable ER in the papilloma




Papillae with no myoepithelial cells (no nuclear p63)

PAPILLARY DUCTAL CARCINOMA IN SITU

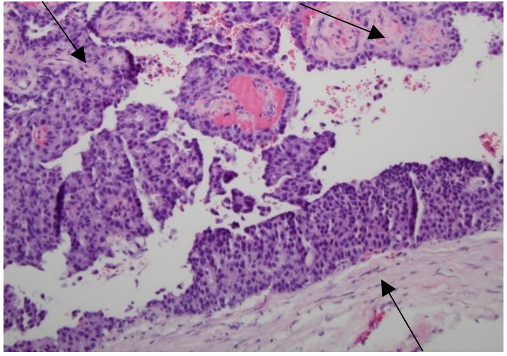
MORPHOLOGY

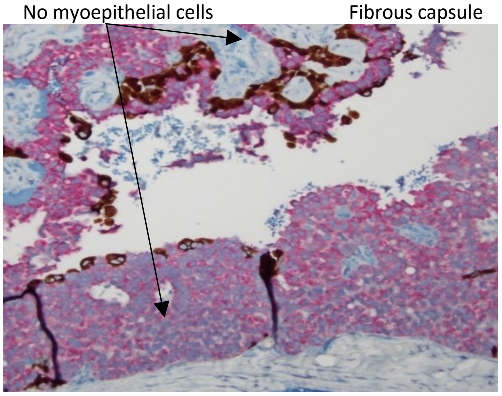
- **Monotonous clonal ductal** epithelial **cells** lining **arborizing filiform fibrovascular cores** that are **devoid** of **myoepithelial cells**
- **Nuclei can be variable** based on grade and are round to oval, have regular or irregular nuclear contours, and conspicuous or inconspicuous nucleoli
- The **duct containing** the **neoplasm** has **preserved myoepithelial cells** (which is different than the papillary fronds that lack myoepithelial cells)
- Neoplasm **may be deceptively bland** with stratified spindled cells, compact columnar cells, or clear cells

OTHER HIGH YIELD POINTS

- The **comedo pattern** is the **only clinically relevant pattern**
- Neoplasm is **graded based** on the **nuclear** cytologic **features**
- **Graded** based **on nuclear morphology**
  - **Low grade:** Think "**small bland**" monomorphic cells
  - **Intermediate grade:** Features between low and high-grade DCIS
  - **High-grade**: Think "**ugly and pleomorphic**" cells
- Immunohistochemistry
  - Myoepithelial cells: Positive for p40, **p63**, **CK5/6**, **calponin**, SMH
  - Ductal cells: **Positive** for **CK7/18 (luminal), p120** (strong membranous), E-cadherin; **Negative** for **CK903** (34βE12), CK5/6, CK14
  - Prognostic markers: ER and PR must be performed

Path Presenter





BNC-5 stain showing (+) CK7/18, (-) p63 and (+/-)CK5/6

ENCAPSULATED PAPILLARY CARCINOMA

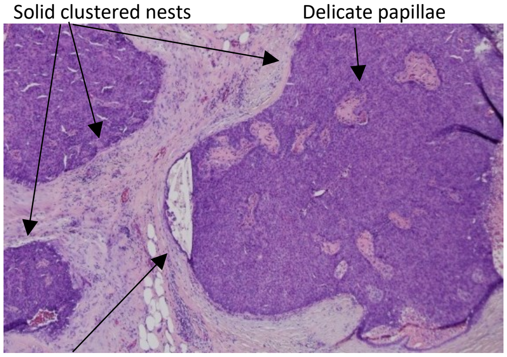
MORPHOLOGY

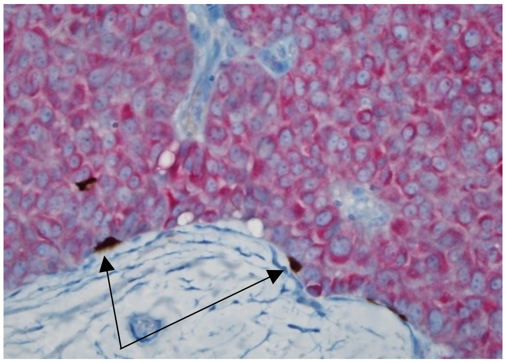
- Carcinoma composed of **fine fibrovascular (papillary) fronds** covered by **neoplastic** epithelial **cells** of **low to intermediate** nuclear **grade**
- Carcinoma is most often in a **cystic space** with surrounding **fibrous capsule**
- **No myoepithelial cells** are present **in** the **fibrovascular fronds** or at the **periphery of cystic space**

OTHER HIGH YIELD POINTS

- WHO recommend **classification as a Tis lesion** (similar to DCIS) **but** is **lacking** the **myoepithelial cells**
- If there is **invasion past the capsule**, then **use** area of **invasion for T classification**
- **Very low risk of metastasis** and a very **favorable prognosis** (>95%, 10-year)
- No need to sample lymph nodes if stromal invasion absent
- **Pitfall:** If there are **isolated tumor cells**, consider **displaced epithelial cells** from biopsy procedure **rather than true invasion** unless absolutely sure
- Most **frequently seen** in **older post-menopausal females** and presents as a **centrally located**, well-circumscribed **palpable mass** (+/- nipple discharge)
- Immunohistochemistry
  - ➢ Myoepithelial cells: **Negative** for **p63** (most useful)
  - ➢ Ductal cells: **Positive** for **CK7/18**; **Negative** for CK5/6 (except high-grade lesions)
  - ➢ Prognostic markers: Nearly all positive for ER and PR; HER-2 negative
- Molecular: **PIK3CA hotspot mutations** seen in about **20% of cases**

Path Presenter





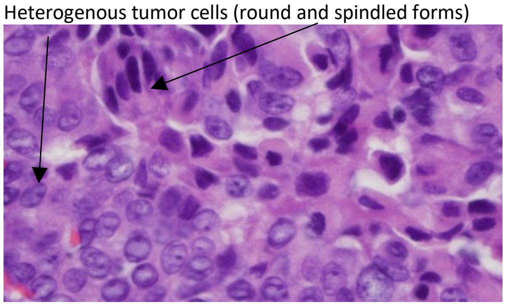
SOLID PAPILLARY CARCINOMA

MORPHOLOGY

- **Heterogenous** or **monotonous round to spindled-shaped** epithelial **cells** with mild to moderate nuclear atypia, and eosinophilic, granular cytoplasm lining delicate papillae
- Arranged in **multiple clustered** and **circumscribed solid nests**
- **Myoepithelial** cells may be **sparse** but are present
- Mitoses are seen and there is **variable mucin** within cytoplasm or lumens
- May have **neuroendocrine differentiation** in approximately **45% of cases**

OTHER HIGH YIELD POINTS

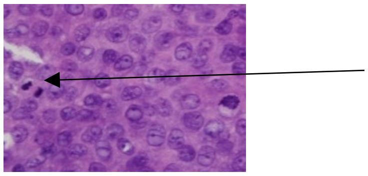
- **Uncommon** and composes <1% of all breast carcinomas
- Typically, it is seen in **older females** with a palpable **multinodular mass**
- Associated with a **good prognosis**
- If **entirely well-circumscribed nodules** (even in absence of myoepithelial cells) are present and no invasion is present
  - ➢ Solid papillary carcinoma in situ
  - ➢ Utilize the **AJCC Tis classification** (similar to DCIS)
- If **infiltrating strands** or **ragged borders** are present
  - ➢ **Solid papillary carcinoma with invasion** or **invasive solid papillary carcinoma**
  - ➢ Utilize the AJCC T classification for the area of invasion
- Immunohistochemistry
  - ➢ Myoepithelial cells: Positive for **p63**, p40, calponin, SMH
  - ➢ Ductal cells: **Positive** for **CK7/18**; **Negative** for CK5/6; variable neuroendocrine expression (synaptophysin, INSM-1, chromogranin)



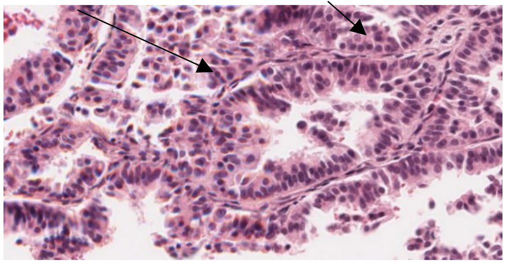
Heterogenous tumor cells (round and spindled forms)

  - Prognostic markers: Almost **all positive** for **ER/PR**; **Her-2 negative**
- Molecular findings
  - **PIK3CA** hotspot mutations seen in approximately **25-35% of cases**
  - **Copy number changes**: Gains in 1p and 16q, losses in 16q

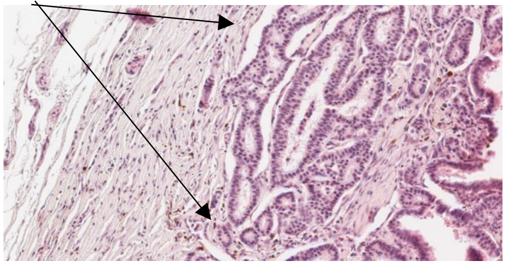
Path Presenter



Mitoses



Fibrovascular cores Monotonous cells



Invasion

INVASIVE PAPILLARY CARCINOMA

MORPHOLOGY

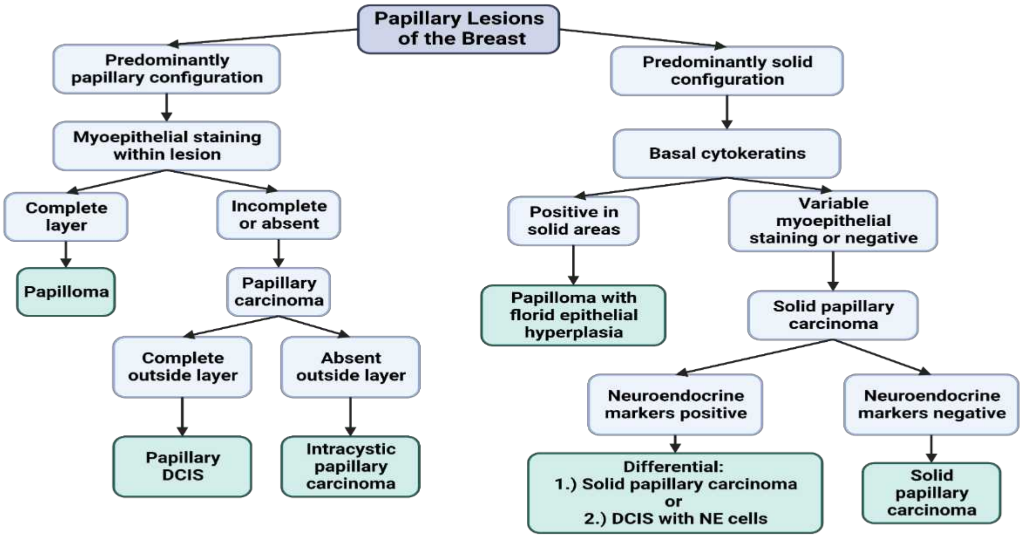
- **Monotonous** neoplastic epithelial cells with **low to intermediate grade nuclei** that are **round** to **oval** with **variable chromatin** distribution, **occasionally** conspicuous **nucleoli** arranged on **fibrovascular cores** with **delicate vessels**
- Usually are **poorly circumscribed** and have an **infiltrative growth** pattern
- **Absence** of **myoepithelial cells**
- **Stromal desmoplastic response** where infiltration occurs at periphery

OTHER HIGH YIELD POINTS

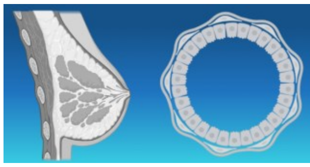
- **Extremely rare** breast carcinoma (<1% of all breast carcinomas)
- Most common in **post-menopausal women** but can be seen in **men**
- **Differential diagnosis** includes **metastasis** (**lung, ovary, thyroid**), solid papillary carcinoma, invasive solid papillary carcinoma, encapsulated papillary carcinoma, and invasive micropapillary carcinoma
- Immunohistochemistry
  - Prognostic markers: **M**ajority are **positive** for **ER/PR**; **HER2 negative**

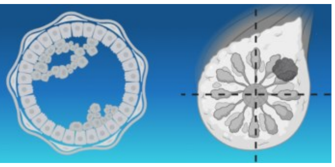
Path Presenter

ALGORITHM TO APPROACH PAPILLARY LESIONS OF THE BREAST


Papillary Lesions of the Breast
Predominantly papillary configuration
Myoepithelial staining within lesion
Complete layer
Incomplete or absent
Papilloma
Papillary carcinoma
Complete outside layer
Absent outside layer
Papillary DCIS
Intracystic papillary carcinoma
Predominantly solid configuration
Basal cytokeratins
Positive in solid areas
Variable myoepithelial staining or negative
Papilloma with florid epithelial hyperplasia
Solid papillary carcinoma
Neuroendocrine markers positive
Neuroendocrine markers negative
Differential: 1.) Solid papillary carcinoma or 2.) DCIS with NE cells
Solid papillary carcinoma

Adapted from: Tse GM et al. The role of immunohistochemistry in the differential diagnosis of papillary lesions of the breast. J Clin Pathol. 2009 May;62(5):407-13.



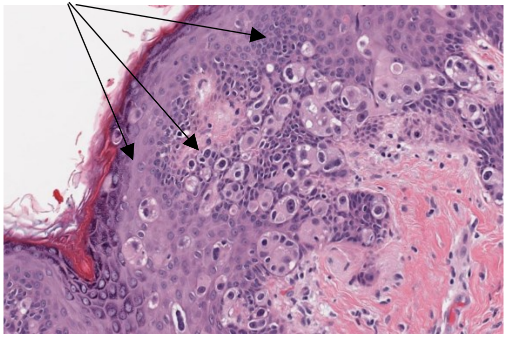


SUMMARY OF PAPILLARY LESIONS OF THE BREAST

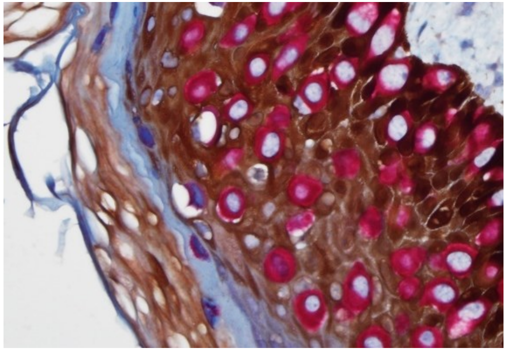
	Intraductal papilloma	Papilloma with DCIS	Papillary DCIS	Encapsulated Papillary Carcinoma	Solid Papillary Carcinoma	Invasive Papillary Carcinoma
Papillary Architecture	• Broad, blunt fronds	• Broad, blunt fronds	• Slender fronds, sometimes branching	• Numerous slender fronds, sometimes branching • Typically, well developed and peripheral; fibrous capsule	• Solid with inconspicuous fibrous septa	• Infiltrative carcinoma with papillary morphology, including fibrovascular cores
Epithelial cells	• Heterogeneous non-neoplastic cells. • Sometimes proliferative lesions (UDH…)	• Focal areas with cytologic features of DCIS (usually Low-grade)	• Entirely occupied by a cell population with features of DCIS (often low-grade)	• Entirely occupied by a cell population with features of DCIS (Often low grade) • Cribriform, micropapillary, and solid patterns may be present, with fusion of papillae	• Entire lesion occupied by a population of cells with low to intermediate grade nuclei • Often spindled or neuro - endocrine morphology.	• Low, intermediate, or, rarely, high grade nuclei
Myoepithelial cells in papillae	• Present	• Present in papilloma but may be scant in DCIS component	• Absent	• Absent	• Absent or Present	• Absent
Myoepithelial cells at periphery	• Present	• Present	• Present	• Absent (usually)	• Absent or Present	• Absent
CK5/6	• Positive in myoepithelial cells and UDH	• Positive in myoepithelial and UDH; Negative in DCIS	• Positive in peripheral myoepithelial • Negative in lesion	• Negative	• Negative	• Negative
ER & PR	• Positive, but heterogeneous	• Strong and diffuse in DCIS	• Strong diffuse	• Strong diffuse	• Strong diffuse	• Positive
Other Stains	• None	• None	• None	• None	• Frequent synaptophysin and chromogranin expression	• None

DISEASES OF THE NIPPLE

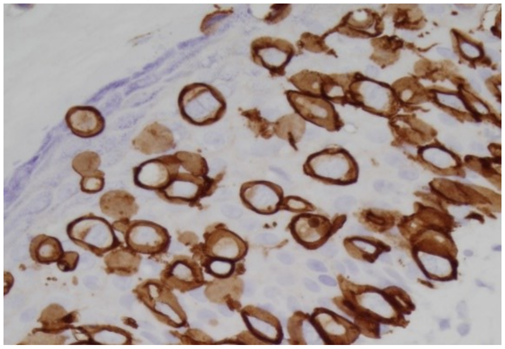
“Buck-shot scatter”



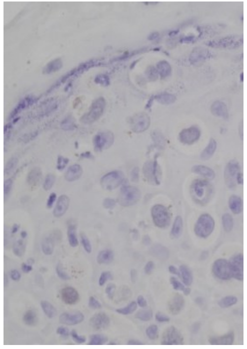
BNC-5 stain showing clonal CK expression in tumor cells



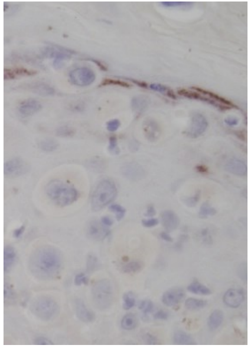
HER-2 IHC highlighting “Buckshot scatter” of tumor cells



ER negative tumor cells



PR negative tumor cells



Path Presenter

PAGET DISEASE OF THE BREAST (MAMMARY PAGET DISEASE)

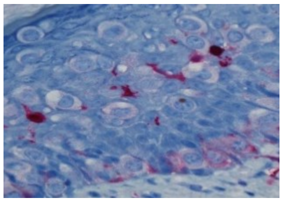
MORPHOLOGY

- **Intraepidermal proliferation** of malignant glandular **epithelial** cells with a “**buckshot scatter**” (transepidermal distribution) appearance
- Malignant cells have **large nuclei**, **prominent** conspicuous **nucleoli**, and abundant **pale eosinophilic cytoplasm**
- Malignant cells can be in **clusters** or **singly**
- May **form glandular structures** and **may contain mucin**
- Often has an associated **lichenoid lymphocytic infiltrate** in papillary dermis

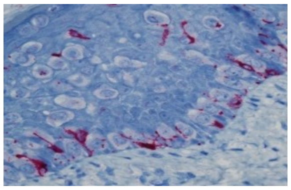
OTHER HIGH YIELD POINTS

- **Uncommon presentation** of breast cancer and is seen in **women and men**
- Presents as a **pruritic scaling skin crust** with **erythema** (majority of cases), but **can be** a **dark hyperpigmented macule**, and/or it can be **ulcerated**
- Patient may complain of a **moist or wet-breast** due to **extravasation of fluid** from **disrupted tight junctions**
- As many as **50% of patients have no mammographic findings**
- Most cases are a **cutaneous extension of DCIS** or **invasive carcinoma**
  - ➢ Many cases involve lactiferous sinuses of the nipple
  - ➢ If not present, **may be derived** from **Toker cells** or other **adnexal-derived cell** type
- May secondarily invade the dermis in more aggressive
- Approximately **50% of cases associated** with **invasive carcinoma**
- **Prognosis** is **determined** by the **presence of invasive** cancer
  - ➢ Skin **ulceration/erosion**, **dermal invasion**, and **hemorrhage** are **not sufficient** for a AJCC **T4b classification**
  - ➢ Any **tumor cells in the superficial dermis** are **not associated with** any **increased risk** of **metastasis**
  - ➢ Paget disease with DCIS only has a **survival of >95% at 20-years**
- Immunohistochemistry & special stains
  - ➢ Majority are **positive** for **CK7**, Cam5.2, **HER2**, **GATA3** (80%)
  - ➢ **Negative** for **S100** (75% of cases), CK5/6, **MelanA**, **HMB45**, ER, and PR
  - ➢ May be **positive for PASD** or **mucin stains** (shows glandular origin)
- Differential diagnoses: Squamous cell carcinoma in situ (Bowen Disease), Melanoma, Toker cell hyperplasia, clear cell change in keratinocytes, sebaceous carcinoma, or carcinoma directly involving the skin

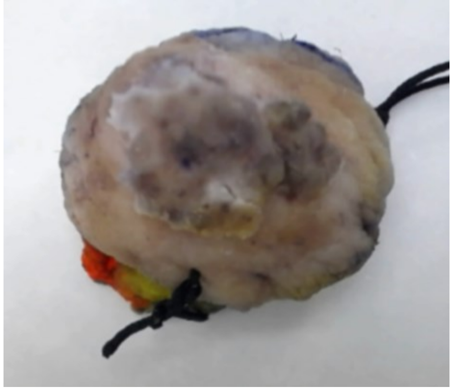
HMB45 negative tumor cells



S100 negative tumor cells



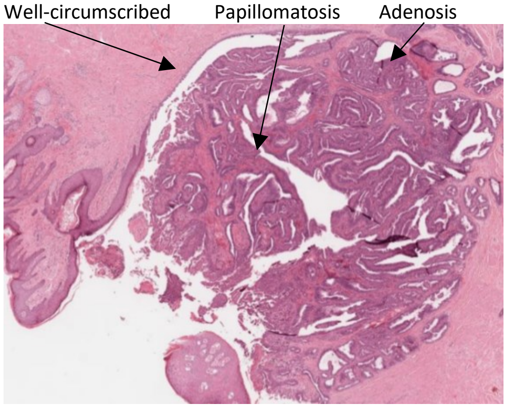
Gross excision showing scaling and crusts involving nipple and areola

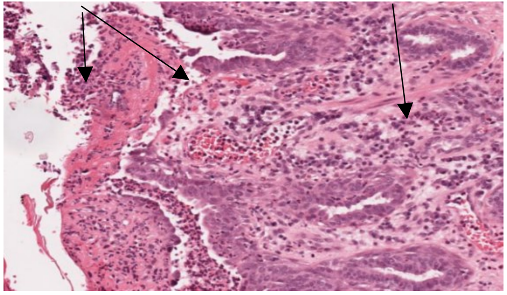


USEFUL SMALL IHC PANEL FOR PAGET DISEASE AND MIMICS

	Paget Disease of Beast	**Toker cell hyperplasia**	**SCC in situ (Bowen Disease)**	**Melanoma**	**Sebaceous carcinoma**
CK7 or Cam5.2	**Positive**	Positive	**Negative**	**Negative**	Variably positive
CK5/6	Negative	Negative	**Positive**	Negative	Positive
p63	Negative	Negative	**Positive**	Negative	Positive
S100	Negative	Negative	Negative	**Positive**	Negative
MelanA/MART1	Negative	Negative	Negative	**Positive**	Negative
HMB45	Negative	Negative	Negative	**Positive**	Negative
ER	**Usually negative**	**Positive**	Negative	Negative	Variably positive (30%)
Her2	**Strong positive**	Strong positive	Negative	Negative	Variably positive (35%)
Adipophilin	Negative	Negative	Negative	Negative	**Positive**

NIPPLE ADENOMA





MORPHOLOGY

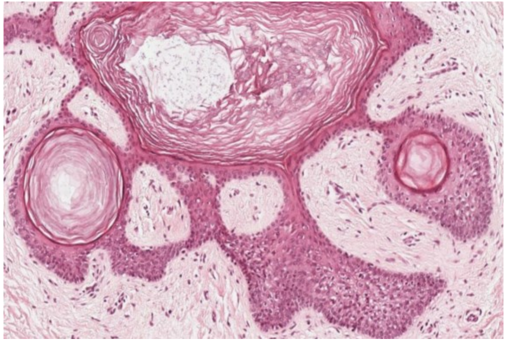
- **Benign, epithelial proliferation composed** of any or a **mixture of**:
  - Simple **ducts**
  - **Papillomatosis** or sclerosing papillomatosis
  - **Adenosis**
  - **Usual duct hyperplasia** or florid hyperplasia
- Epidermis **may have Toker cell hyperplasia** or **hyperkeratosis**
- **Myoepithelial** cells **surround** all the **ducts**
- May have **epidermal erosion** and/**or hemorrhage**, or **focal necrosis**
- Often **well-circumscribed** lesion, but **stromal fibrosis may entrap ducts** in a pattern that **can resemble invasive carcinoma**

OTHER HIGH YIELD POINTS

- **Uncommon** breast lesion that is most often seen in **middle-aged females**
- Patients present with an **irregular or lobulated palpable breast mass** and can have **nipple discharge** and/or be **tender**
- Clinically it **can mimic Paget disease** due to the erythema, hyperkeratosis and crusts, and erosion/ulceration
- Benign lesion but **can reoccur without complete excision** of the lesion
- Molecular: **PIK3CA present** in **half of** all **cases**
- Main significance is not to confuse it with invasive carcinoma

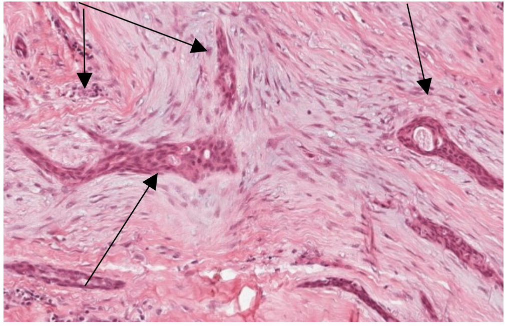
Path Presenter

SYRINGOMATOUS TUMOR



MORPHOLOGY

- **Benign infiltrative neoplasm** composed of **tubules**, solid **nests**, and **cysts**
- The tubules are **composed of more than one cell layer** that usually are cuboidal (glandular) or flattened (squamous)
- The **tubules often display branching** and have **eosinophilic luminal secretions**
- **Squamous metaplasia** can be solid or cystic and are frequently "**tadpole**" or "**comma**" shaped
- **Cystic spaces** are **filled with orthokeratin**
- Tumor frequently **infiltrates around bundles of smooth muscle**, **lactiferous sinuses** and may have **perineural invasion**
- **No necrosis** and **mitoses** are **extremely rare** (if any)


Infiltrative appearance
"Tadpole"
Dense fibrosis

- **Stroma is variable** and can be myxoid, hyaline, fibrous, or loosely cellular and is denser around the tumor nests
- May have **pseudoepitheliomatous hyperplasia** or **lymphocytic infiltrate**

OTHER HIGH YIELD POINTS

- **Very rare tumor** occurring almost exclusively in middle-aged females
- Presents as a **palpable** firm **mass** in the dermis of the **nipple/areola**
- **Recurrence occurs in 30%** of cases that have a positive margin
- Immunohistochemistry:
  - Glandular: Positive for CK8/18
  - Squamous: Positive for p63, CK10
  - Myoepithelial-like cells: Positive for p63
  - Negative for ER, PR, and HER2

Path Presenter

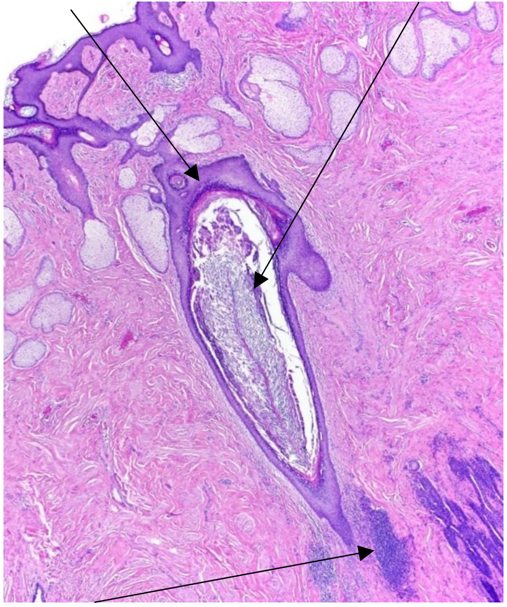
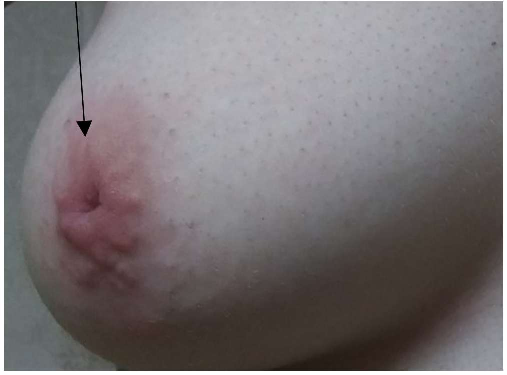

Squamous epithelium
Entrapped keratin debris
Chronic inflammation

Image credit: Dr. Patrick J. McIntire, MD


Inverted nipple

Provided by LizArranda on Wikimedia Commons

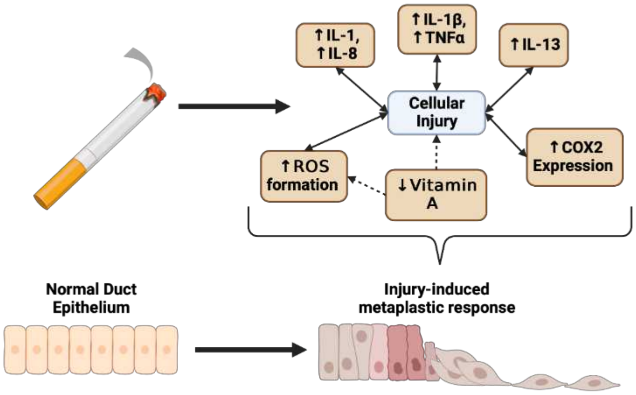
SQUAMOUS METAPLASIA OF THE LACTIFEROUS DUCTS ("SMOLD")

MORPHOLOGY

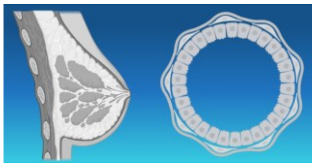
- Duct epithelium with **squamous metaplasia** and **entrapped keratin**
- Often has **acute** and **chronic inflammation** surrounding nests
- **Giant cells may be present adjacent to the duct space and is** more common when keratin debris is present in the stroma
- Chronic **fibrosis** may be seen from prolonged **chronic inflammation**
- **Bacteria can be present** if there is a **secondary infectious** etiology

OTHER HIGH YIELD POINTS

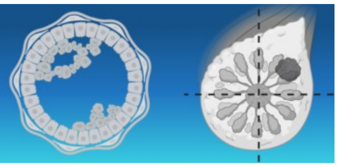
- **Occurs at any age >20 years** and is seen in **females and males**
- This entity is essentially a **special form** of **duct ectasia**
- Presents as a **very painful** and **erythematous subareolar mass** that is **sterile** (no organisms)
- **Highly associated with tobacco use** and **inverted nipples** as nearly all patients have history of both
- Proposed **hypothesis** for the findings are:
  - **Squamous metaplasia** is caused by the **toxins from** the **tobacco** and mediating a **vitamin A deficiency** and thus **causing** the **metaplasia**
  - **Inverted nipples** are caused by the **recurrent inflammation** and **fibrosis** surrounding the duct
- Surgical intervention (wedge resection) is the main treatment but may cause fistula track near the areolar perimeter


↑IL-1,
↑IL-8
↑IL-1β,
↑TNFα
↑IL-13
Cellular Injury
↑ROS formation
↓Vitamin A
↑COX2 Expression
Normal Duct Epithelium
Injury-induced metaplastic response

Pathogenesis of SMOLD



2. BREAST PATHOLOGY



INVASIVE BREAST CARCINOMA

GENERAL BACKGROUND

- **Most common cancer in women** and **leading cause of** female **cancer death** worldwide
- Presenting signs and symptoms:
  - **Unscreened populations:** Mass, skin erythema and edema due to cancer in dermal lymphatics
  - **Screened populations:** Spiculated mass, architectural distortion, MRI enhancement
- **Three pillars of diagnosis:** Physical exam, imaging, needle biopsy/cytology
  - **When** these are **concordant**, the **risk of missing breast cancer is extremely low** but requires careful correlation
- **General risk factors:** Increased estrogen, seen with early menarche, fewer children, less lactation, and obesity, increased alcohol consumption

PATHOGENESIS AND MOLECULAR BASIS

- **Two main pathways** separated by Estrogen Receptor (ER) status:
  - **ER-positive (ER+, HER2-):** Diploid with specific chromosomal gains/losses (e.g., gain 1q, loss of 16q) and are usually low to intermediate-grade cancers
  - **ER-Negative (ER-, HER2+/-):** Aneuploid with complex karyotypes, frequent TP53 mutations, and are most frequently high-grade tumors with high proliferation rate
- Both pathways show **PIK3CA mutations**, but it is **more common in ER-positive** tumors
- **Non-obligate precursors to ER (+) cancers:** FEA, ADH, and low-grade DCIS
- **Non-obligate precursors ER (-) cancers:** Microglandular adenosis and high-grade DCIS

MOLECULAR CLASSIFICATION (BASED ON HIERARCHICAL CLUSTER ANALYSIS OF GENE EXPRESSION)

	Luminal A	**Luminal B**	**HER2-Positive**	**Basal type**
Percent of all tumors	50%	20%	15%	15%
Classic ER/HER2 status	ER+, HER2-	ER+, HER2-	ER-, HER2+	ER-, HER2-
Ki-67	Low	Intermediate	High	High
Actual ER/HER2	**ER+**		**HER2+**	Triple negative
Grade	**Low**			**High**
Recurrence Risk	**Low, but long term**			**High, but short term**
Therapies used	**Hormone Rx**		**HER2 Rx**	**Chemotherapy**

* Note: Other molecular classifications exist and include additional/alternate groupings; this is just the most well established frequently utilized

GRADING

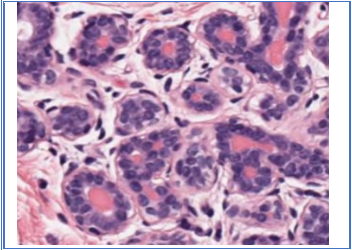
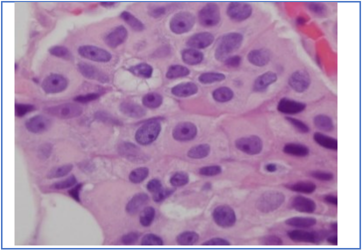
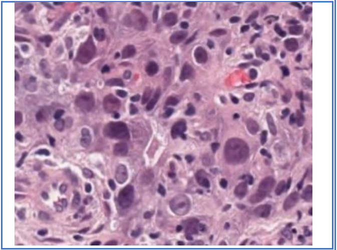
- Grade using the **Nottingham system** based on 3 characteristics:
  - **Tubule formation:** Only structures with central lumina surrounded by polarized cells are counted
  - **Nuclear pleomorphism:** Assessed in the area showing the worst cytologic atypia
  - **Mitotic count:** Assessed in mitotic hot spot. Remember to factor in your field area

Tubule Formation	**Score**	**Nuclear Pleomorphism**	**Score**	**Mitosis**	**Score**
Majority of tumor (>75%)	1	**Small, regular, uniform** (<1.5x the size of normal nucleus)	1	$<3/\text{mm}^2$	1
Moderate degree (10-75%)	2	**Moderate increase in size/variability** (1.5-2x cell size)	2	$4\text{-}7/\text{mm}^2$	2
Little or none (<10%)	3	**Marked variation** (>2x cell size), vesicular chromatin, prominent nucleoli	3	$\geq 8/\text{mm}^2$	3

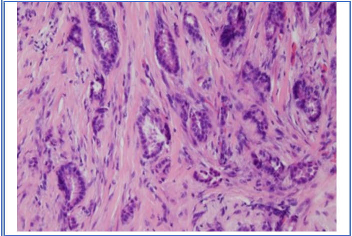
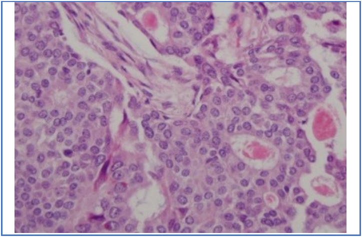
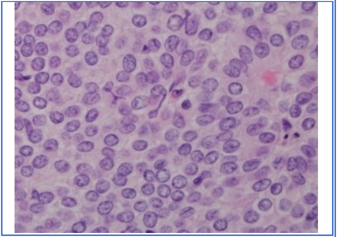
Total Nottingham Score	**Grade**
3-5	1
6 or 7	2
8 or 9	3

NOTTINGHAM GRADING EXAMPLES

NUCLEAR PLEOMORPHISM

NORMAL / SCORE 1	SCORE 2	SCORE 3
		

TUBULE FORMATION

SCORE 1	SCORE 2	SCORE 3
		

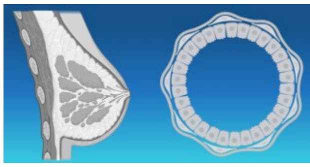
GENERAL IHC

- **Invasive cancers** usually **stain with LMWCK** (including CK7 and CK19), EMA, and **GATA3**
- Some cancers (often the **well-differentiated** ones) **stain** with **GCDFP-15(BRST2)** and **mammaglobin**
- Higher-grade **triple-negative cases stain** with **basal markers** including **HMWCK** (CK5/6)
- A subset of cancers (often **metaplastic** and/or triple negative) express **S100**, **SOX10**, and/or **p63**
- **TRPS1 will stain all breast cancers except apocrine** adenocarcinoma

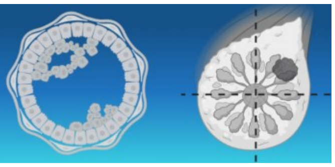
MYOEPITHELIAL CELL MARKERS

Marker	Clone	Staining pattern	Comment
p63	4A4	Nuclear	• One of the **most sensitive** and **specific** markers • Normal ducts show **continuous dot-like pattern** • **In situ** carcinomas are **focally discontinuous** • Attenuated or **non-reactive in invasive** & **papillary carcinoma**
SMMHC	SMMS-1	Cytoplasmic	• **More sensitive than p63** • Some **cross-reactivity with vascular smooth muscle cells** and **stromal myofibroblasts** (but less than calponin) • Linear cytoplasmic pattern with **gaps in the in-situ carcinoma**
Calponin	EP798Y	Cytoplasmic	• Linear cytoplasmic pattern with **gaps in the in-situ carcinoma** • **Higher frequency** of **cross-reactivity** to vascul**ar smooth muscle cells** and stromal **myofibroblasts** • **Reactive to** small proportion of **tumor cells**
SMA	1A4	Cytoplasmic	• **Sensitive** but **not a specific marker** due to the **marked cross-reactivity** to **vascular smooth muscle cells** and **myofibroblasts**
Maspin	G167-70	Nuclear, cytoplasmic	• **Very sensitive marker** and **lacks the cross-reactivity** to vascular smooth muscle cells and stromal myofibroblasts • **Reacts to tumor cells**, which **limits the utility** of this marker
CD10	56C6	Cytoplasmic, membranous	• **Somewhat sensitive marker** but has **cross-reactivity** to **stromal myofibroblasts**, **non-specific reactivity** to **epithelial cells**, but **no reactivity** to **vascular smooth muscle cells**

Adapted from: Liu H. Application of Immunohistochemistry in Breast Pathology: A Review and Update. Archives of Pathology & Laboratory Medicine: December 2014, Vol. 138, No. 12, pp. 1629 1642.



2. BREAST PATHOLOGY



IS IT INVASIVE OR A MIMIC?

- **Invasive** breast is **defined by** the **absence of** peripheral **myoepithelial cells**
- Stains for myoepithelial cells should be employed as part of a panel or cocktail with at least one nuclear and one cytoplasmic stain
- **Do not rely** solely **on negative myoepithelial stains** to diagnose invasion, H&E findings must be concordant
- Nests of **in situ carcinoma may** be **surrounded by reduced numbers** or **weakly staining** of **myoepithelial cells**

MORPHOLOGIC FEATURES OF CANCER VERSUS MIMICS

Feature	Invasive cancer	Complex Sclerosing lesions	DCIS involving sclerosing adenosis
Stroma	Desmoplastic	Dense	Dense
Cytology	Atypical	Bland	Atypical
Gland profile	Angulated	Compressed	Solid/Cribriform
Architecture	Infiltrative	Lobulated	Lobulated
Myoepithelial cells	Absent	Present	Present

Modified From: Peng et al. Update on Immunohistochemical Analysis in Breast Lesions. Archives of Pathology & Laboratory Medicine: August 2017, Vol. 141, No. 8, pp. 1033-1051.

SUBTYPES OF INVASIVE CARCINOMA

NO SPECIAL TYPE (NST)

Invasive ductal carcinoma
Medullary pattern
Osteoclastic-like giant cell pattern
Neuroendocrine differentiation pattern
Pleomorphic pattern
Choriocarcinomatous pattern
Melanotic pattern
Oncocytic pattern
Lipid-rich pattern
Glycogen-rich clear cell pattern
Sebaceous pattern

CARCINOMAS OF SPECIAL TYPE

Non-salivary gland type tumors

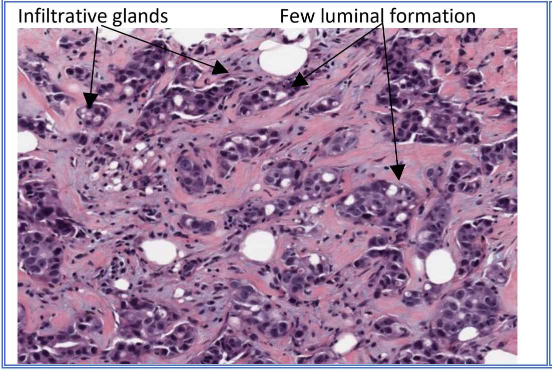
Microinvasive carcinoma
Invasive lobular carcinoma
Tubular & cribriform carcinoma
Mucinous (colloid) carcinoma
Mucinous cystadenocarcinoma
Invasive papillary carcinoma
Invasive micropapillary carcinoma
Metaplastic carcinoma
Low-grade Adenosquamous carcinoma
Triple-negative and Basal-like carcinoma
Inflammatory carcinoma
Invasive apocrine carcinoma
Neuroendocrine tumor (NET) and carcinoma

Salivary gland-type tumors

Acinic cell carcinoma
Adenoid cystic carcinoma
Secretory carcinoma
Mucoepidermoid carcinoma
Polymorphous adenocarcinoma

Note: Tumors showing a special histologic pattern in ≥ 90% of the tumor are designated as pure special tumor. If less than 90%, they are designated as "No Special Type" (NST), which accounts for the majority of breast cancer cases. If a special type composes 10-90% of the carcinoma, it is reported as a "Mixed invasive breast carcinoma of no special type and special subtype".

INVASIVE CARCINOMA OF NO SPECIAL TYPE



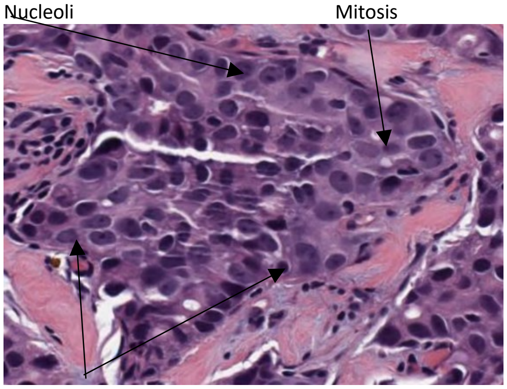
INVASIVE "DUCTAL" CARCINOMA

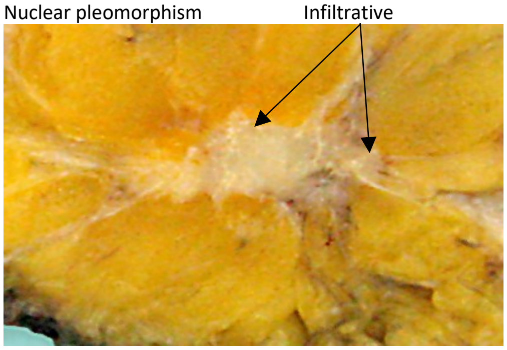
GENERAL MORPHOLOGY

- Composed of infiltrative **malignant epithelial cells** that can be in **irregular and stellate glands**, **cribriform** pattern, **solid**, or **small clusters**
- **Morphology is variable** based on if there are any morphologic patterns
- **No myoepithelial cells** surround any of the tumor cells
- **May infiltrate lymphovascular** channels **or** have **perineural invasion**
- Often has a **desmoplastic stromal response** to the infiltration of tumor cells
- **Necrosis and calcifications** may or **may not be present** in the lesion
- May have biopsy site changes (granulation tissue etc.)

OTHER HIGH YIELD POINTS

- **Represents** approximately **75% of invasive** breast **carcinomas**

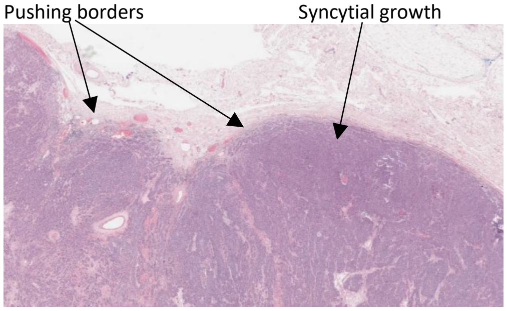


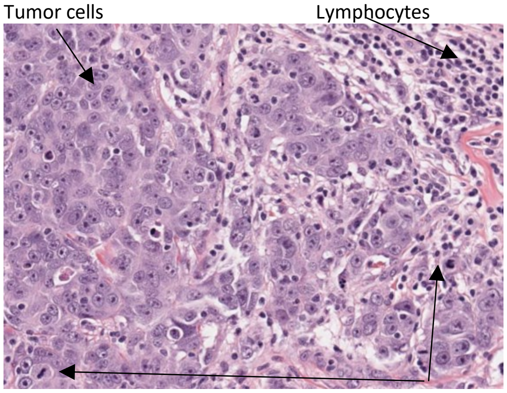


- The **grade** of carcinoma is **based on the Nottingham** grading **scale**
- Can present as a hard lump/mass within the breast if it is at least 2cm in size
- **Nearly 90% of call palpable cancers are identified by the patient** themselves with the remainder detected by examination
- Patients are **usually middle-aged females** and **only 1% of cases** occur **in males**
- **Immunohistochemistry is dependent on the specific subtype** but those with no morphologic patterns:
  - **Ductal cells:** Positive for LMWCK (CK8/18, CKAE1/AE3, CK7), p120, e-cadherin, TRPS1, GATA3 (variable on HR status), variable positivity for HMWCK (CK5/6, CK14, CK17), SOX10 (variable)
- **Prognostic markers** should be **performed on all invasive carcinomas**
  - **Report the % of tumor cells positive and** the **intensity** of staining
- Molecular:
  - **ER-positive:** Gains of 1q and loss of 16q
  - **ER-negative:** Gain of 11q13, loss of of 13q, amplification of 17q12
  - **HER2-amplification** is seen in **approximately 15% of cases** but allows for targeted therapy albeit toxic
  - **PIK3CA and ESR1** mutations are **associated with endocrine therapy resistance**
- **Gene expression profiles:** Helpful to classify if they are luminal A, luminal B, HER2-enriched, triple-negative/basal-like
  - Majority of **low-grade NST** cases are **luminal A subtype**

Path Presenter

INVASIVE CARCINOMA OF NST WITH MEDULLARY PATTERN





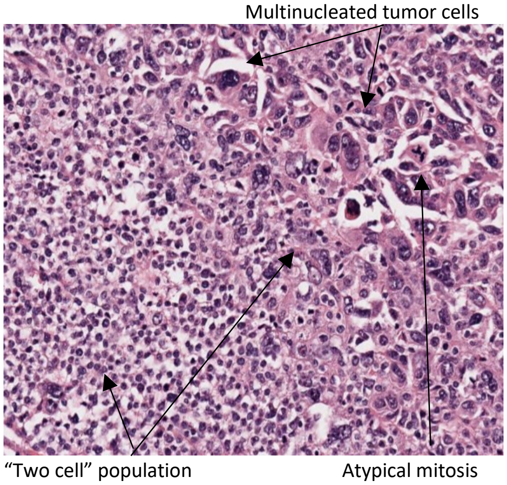
GENERAL MORPHOLOGY

- **Well-circumscribed**, high-grade carcinoma with "**pushing margins**"
- Tumor cells have **high-grade nuclei** have a **syncytial** (sheet-like) **architecture** with **no glandular formation** in any part of the tumor
- **Prominent** tumor **infiltrating lymphocytes** between the tumor cells and at the periphery of the tumor
- **Mitoses can be seen** throughout the tumor
- **Dense fibrous tissue surrounds the tumor** and desmoplasia may be present

OTHER HIGH YIELD POINTS

- Presents in **younger females** (usually age 50) as a **soft, palpable circumscribed mass**
- May have **palpable lymph nodes but** it is **from hyperplasia**
  - **Nodal metastasis** is **not common**
- **Better outcome** than other stage-matched high-grade cancers
  - Hypothesized to be due to the tumor infiltrating lymphocytes
- IHC: **Epithelial cells** are **positive** for **CK5/6, CK14, EGFR, p53**, and **PDL1** expression (more than 80% of cases)
- **Prognostic markers**: Majority are **triple negative** (basal-like)
- **Molecular**: About **15% of patients are BRCA1** mutation **carriers**
- **Differential diagnoses**: Metastatic high-grade carcinoma from other organ and lymphoma

Path Presenter



INVASIVE CARCINOMA OF NST WITH CHORIOCARCINOMATOUS FEATURES

GENERAL MORPHOLOGY

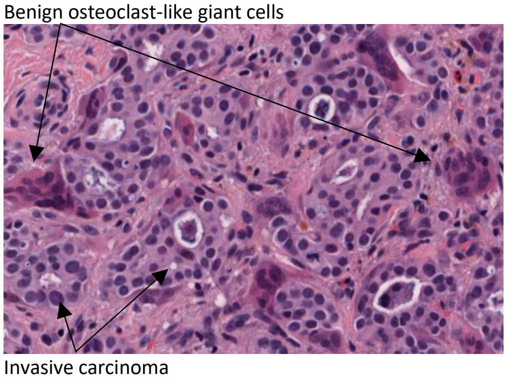
- **Markedly pleomorphic tumor cells** that appear as **two different populations**
- **Large, pleomorphic**, and **multinucleated tumor cells** have **smudged nuclei**, **eosinophilic cytoplasm** with **occasional vacuoles**, and **irregular cytoplasmic projections**
- Second tumor cell population is **monocytoid in appearance**
- Scattered, **highly atypical mitoses** are seen throughout

OTHER HIGH YIELD POINTS

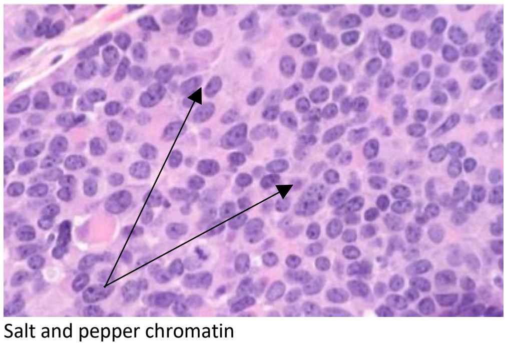
- **Extremely rare** morphologic pattern of invasive carcinoma with NST
- May have an **elevated β-hCG**, but **nearly 60% of patients with IC-NST** also **have this**, so this is a **non-specific finding**
- All cases have been seen in women and are **middle-aged** to **elderly**
- IHC: Often **positive for hPL** and **β-hCG; negative** for **ER** and **PR**

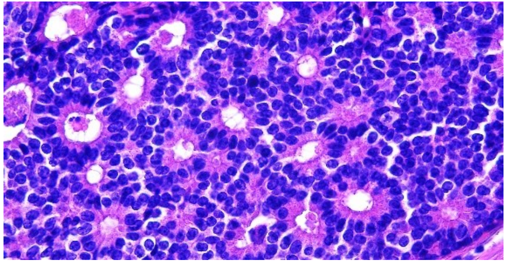
Path Presenter

Osteoclast-like giant cell pattern



Neuroendocrine pattern





OTHER RARE MORPHOLOGIC ENTITIES OF INVASIVE CARCINOMA OF NST

- **IC-NST with osteoclast-like giant cells – Giant cells** are **similar to histiocytes** and **osteoclasts** and **are benign**, lesion is associated with hypervascular stroma with surrounding hemosiderin and hemorrhage; associated with **any histologic type of carcinoma**

- **Neuroendocrine differentiation pattern – Any carcinoma** with **salt and pepper chromatin,** variable conspicuous nucleoli, eosinophilic cytoplasm, for which **lacks the features** to be called **a neuroendocrine carcinoma**; **stain with** some **neuroendocrine markers** (synaptophysin, chromogranin, INSM-1); frequently are **ER-positive** and **HER2-negative**

- **Oncocytic pattern –** Carcinoma cells have **increased** numbers of **mitochondria** which make the **cytoplasm granular and eosinophilic**

- **Melanotic pattern –** The carcinoma cells are reminiscent of melanoma; can be cohesive, epithelioid, spindled, binucleated, conspicuous nucleoli, have dusty eosinophilic cytoplasm, produce melanin pigment

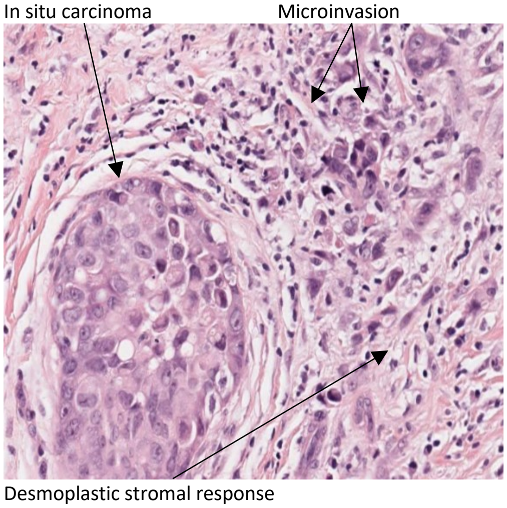
- **Pleomorphic pattern –** The tumor cells have marked pleomorphism, often have multinucleation

- **Lipid-rich pattern –** The tumor cells have **abundant intracytoplasmic lipid** which are positive for **Oil Red O** or **Sudan** (both **require fresh tissue**, FFPE eliminates the lipid); commonly are **grade 3** carcinomas which are **ER-negative**, **PR-negative**, and **HER2-positive**

- **Glycogen-rich pattern –** The tumor cells have abundant intracytoplasmic glycogen stores which are **PAS-positive** and **diastase resistant**

- **Sebaceous pattern –** The tumor cells can be oval to round and have vacuolated, clear cytoplasm, and have nuclei that are irregularly-shaped; intracytoplasmic lipid is **positive** for **Oil Red O**

INVASIVE CARCINOMA OF SPECIAL TYPE (NON-SALIVARY GLAND TYPE)



MICROINVASIVE CARCINOMA

MORPHOLOGY

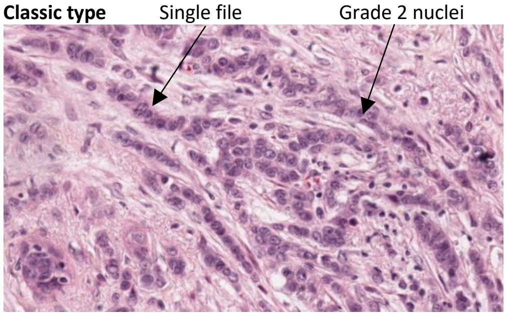
- **Invasive carcinoma that is ≤ 1mm in size**, often **adjacent to high-grade DCIS**
- **Earliest recognizable forms** of **invasive** carcinoma that presents as:
  - **Invasion beyond myoepithelium**
  - **Small, angulated clusters** of tumor cells infiltrating stroma
  - Associated with **desmoplastic stroma** changes

OTHER HIGH YIELD POINTS

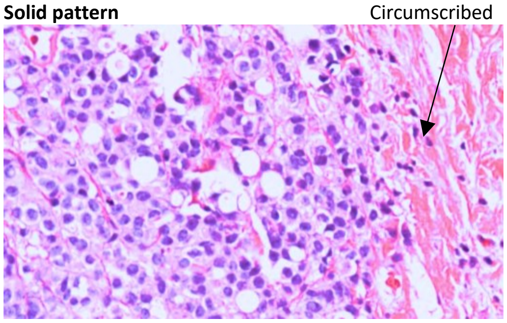
- **Better prognosis than larger invasive** tumors
- **Often multifocal** and if any single **invasive focus is > 1mm then** it is called **invasive carcinoma** (not microinvasive)
- Be **wary diagnosing** this **on** a **biopsy** as more **invasion may be on excision**
- Best practice is to **get levels** to **exclude any larger focus** of invasive carcinoma

Path Presenter

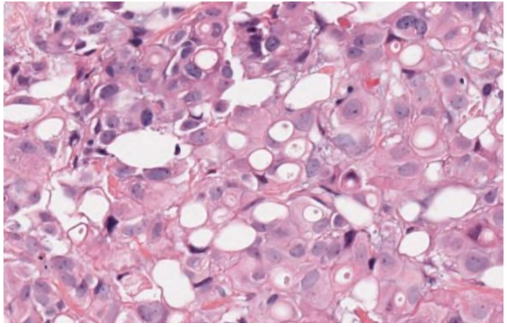
Classic type



Solid pattern



Pleomorphic



INVASIVE LOBULAR CARCINOMA

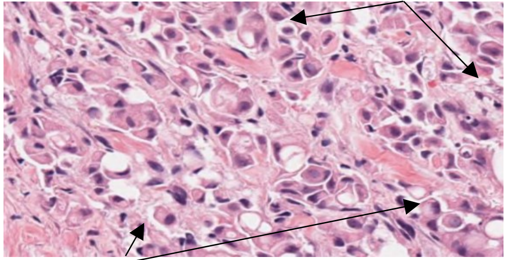
MORPHOLOGY

- Malignant epithelial cells with **variable cytologic features**
- **Classic type** – Tumor cells are discohesive and have **nuclei grade 1 or 2**, **round** nuclear **contours**, and have **scant to moderate cytoplasm**
- **Signet ring cell type** – Tumor cells are **discohesive** and have **eccentrically** located **nuclei** that are **compressed** from the **intracytoplasmic mucin vacuole**
- **Pleomorphic type** – Tumor cells are **discohesive** and **are > 4x that of a lymphocyte** and have **nuclei that are markedly irregular**, conspicuous **nucleoli**, and **variable chromatin**, and **variable cytoplasm**

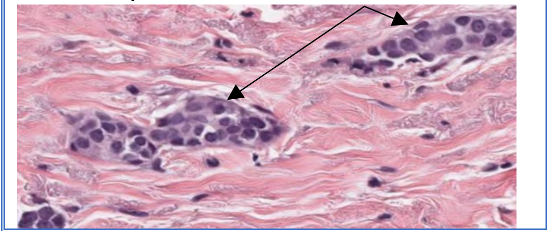
OTHER HIGH YIELD POINTS

- Accounts for nearly **15% of all invasive** breast **carcinomas**
- Presents in women that are **usually middle aged** and **may not be palpable** or is **poorly defined**; may be **seen in males that have BRCA2 mutations**
- Often **little host stromal reaction** or disturbance of background architecture
- Nearly **90% of classic type are Grade 2** tumor **cells**
- **Lymphovascular invasion is very rare** due to the dispersion of single cells
- Growth patterns are variable and can be any of the following:
  - **Classic pattern (most common)** – Single file rows of tumor cells that dissect collagen fibers
  - **Alveolar pattern (~10%)** – Tumor cells are in round aggregates and are separated by a fibrous band and may resemble LCIS
  - **Solid pattern (~5-10%)** – Tumor cells from large, circumscribed nests, mimic lymphoma, and often have the classic pattern at the edges of the nests
  - **Tubulolobular pattern (<1~)** – Tumors have mixtures of classic type and few scattered, miniature round tubules of tumor cells with grade 1 nuclei
  - **Mucinous pattern (rare)** – Tumor cells with signet ring cell morphology and are suspended in extracellular mucin
- IHC: **Positive for cytokeratins**, **GATA3**, **p120** (**cytoplasmic**) AR, ER, PR, MUC1, GCDFP15, and negative for HER2, e-cadherin, CDX-2
- **Special stains:** Intracytoplasmic mucin is **mucicarmine positive**

Signet Ring cell type



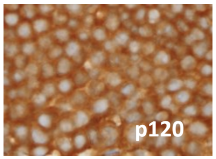
Tubulobular pattern

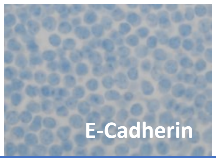


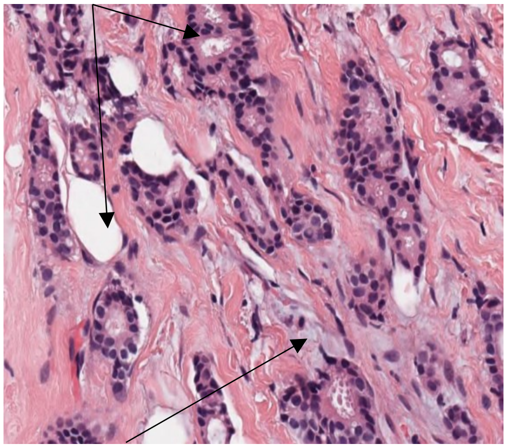
- **Molecular classification:** Majority are **luminal A type**, and second most common is luminal B type
- **Molecular mutations: CDH1** and **PIK3CA** mutations
- **Cytogenetic abnormalities:** Gain of 1q and 16p, and loss of 16q

IHC Stain	Normal Epithelium	Lobular Carcinoma	No Special Type
E-Cadherin	Membrane staining	Negative	Membrane staining
P120	Membrane staining	Cytoplasmic	Membrane staining
β-Catenin	Membrane staining	Absence of membrane staining	Membrane Staining

Path Presenter







TUBULAR CARCINOMA

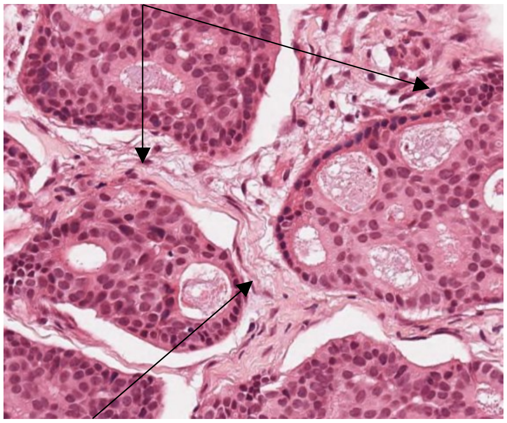
MORPHOLOGY

- **Haphazard proliferation** of **infiltrative tumor cells** that are arranged in **well-formed tubules** with **angled** and **tapered edges** (90% of tumor must have)
- Tumor cells have **low-grade nuclei** with **uniform chromatin distribution**, small **single conspicuous nucleoli**, and **cytoplasm with occasional snouts**
- **Stromal desmoplastic response** is present
- **No myoepithelial cells** surround the tubules

OTHER HIGH YIELD POINTS

- An **uncommon low-grade** invasive **carcinoma** with a **good prognosis**
- Often **associated with a low-grade DCIS component**, CCH, ALH, and FEA
- Often **mimics sclerosing adenosis**, **DCIS**, and **Microglandular adenosis**
- IHC: **Positive** for **ER** and **PR** and **negative for HER2**; negative for myoepithelial markers

Path Presenter



CRIBRIFORM CARCINOMA

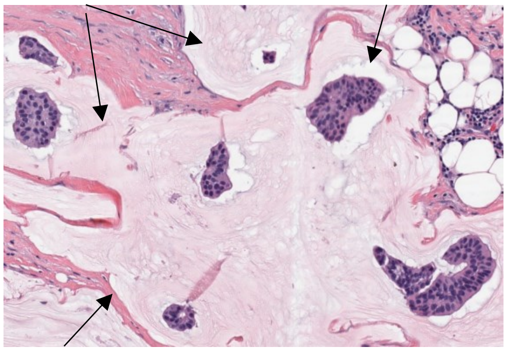
MORPHOLOGY

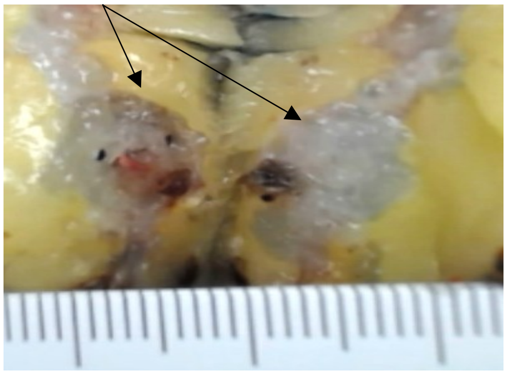
- **Haphazard fenestrated proliferation** of infiltrative **cribriform nests** and **compose > 90% of tumor**
- Tumor cells have **low-grade, polarized nuclei** with **uniform chromatin** distribution, small **single conspicuous nucleoli**, and **eosinophilic cytoplasm**
- **Stromal desmoplastic response** is present
- **No myoepithelial cells** surround the tubules (tumor cells get crushed and appear like myoepithelial cells)

OTHER HIGH YIELD POINTS

- **Rare** and **uncommon low-grade carcinoma** with a **good prognosis**
- IHC: **Positive** for **ER** and **PR** and **negative for HER2**; negative for myoepithelial markers

Path Presenter





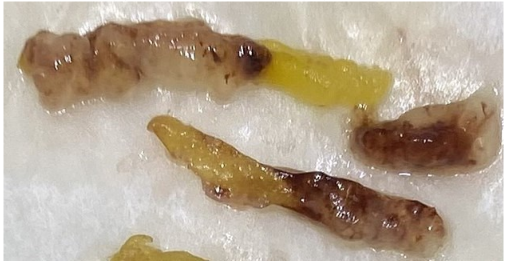

Gelatinous appearance of core biopsy

Image credits: Dr. Mikael Häggström, MD

MUCINOUS CARCINOMA

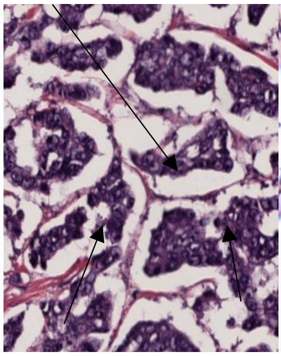
MORPHOLOGY

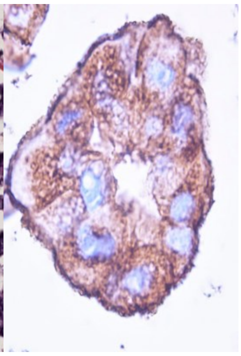
- **Scattered groups** and **nests** of **invasive carcinoma** floating **in pools of extracellular mucin**
- **Delicate fibrous septae** separate the pools of extracellular mucin
- The tumor cells are composed of **low to intermediate-grade nuclei** that are **round to oval**, have **regular chromatin** distribution, and **variable eosinophilic cytoplasm**
- Lesion is **well-circumscribed**

OTHER HIGH YIELD POINTS

- **Uncommon** invasive carcinoma occurring in **elderly women** and presents as a **soft**, **palpable mass** that **mimics** a **benign process**
- Has **three main histologic patterns**:
  - **Pure mucinous carcinoma** – composed of two subtypes, **type A is paucicellular** and **type B is more cellular** and **less mucin**; has a **favorable prognosis**; **type B frequently** has **neuroendocrine differentiation**
  - **Mixed mucinous carcinoma** – has both a **mucinous component** and an **invasive component** which **lacks the mucin component** (>10% of tumor); has an **intermediate prognosis**
  - **Micropapillary mucinous carcinoma** – micropapillary architecture and often has an **inverted appearance** in which the **cytoplasm points towards the outside** of the spherules; has a **worse prognosis** when compared to the other patterns of mucinous carcinoma
- **Prognostic markers**: Majority are **positive** for **ER** and **PR**; negative for **HER2**
- IHC: **Positive** for **WT1**, **EMA**; variable neuroendocrine expression (synaptophysin, chromogranin, CD56, INSM1)
- **Molecular**: Mutations in **GATA3** (~25%), **KMT2C** (20%), **MAP3K1** (~15%), **PIK3CA** (~10%), and **fusion of OAZ1-CSNK1G2** (<5%, recurrent but not pathognomonic)
- **Differential includes** a rare entity called **mucinous cystadenocarcinoma**:
  - Invasive breast cancer characterized by cystic structures lined by tall columnar cells with intracytoplasmic and intracystic mucin, like pancreatic IPMNs or ovarian mucinous carcinoma

Path Presenter




EMA, image credits : Takashi Fujisawa M.D., Ph.D. (@Patholwalker)

INVASIVE MICROPAPILLARY CARCINOMA

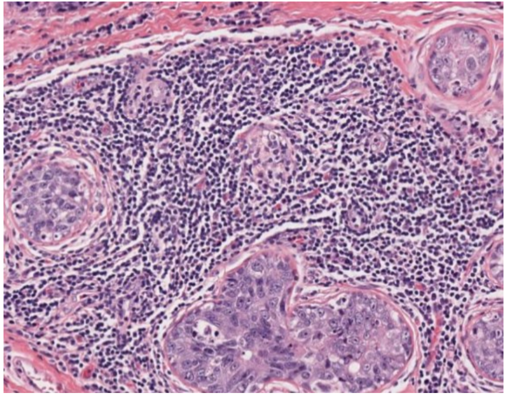
MORPHOLOGY

- The tumor cells can be **cuboidal to columnar** and have **intermediate** to **high-grade nuclei**, with **granular eosinophilic cytoplasm**
- Tumor cells are **arranged in small**, **hollow**, or **morula-like clusters** with an **inside out-growth pattern** and are **surrounded by spaces** with **intercellular fluid** and a **delicate stromal network**
- **No fibrovascular cores** (as is the case with all micropapillary tumors)
- Tumor cells have **reverse polarity** (apical cytoplasm faces outwards)

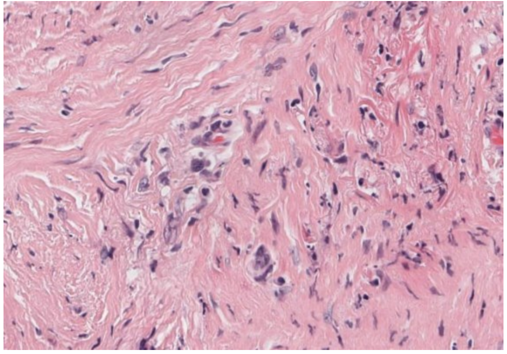
OTHER HIGH YIELD POINTS

- **Very rare** and often occurs in **younger patients** and **affect both sexes**
- **Nearly 67%** of cases **have lymph node metastasis at presentation**
- Despite having tubules, they are **graded as a Nottingham score 3**
- **Survival is not significantly worse** than stage-matched IC-NST
- IHC: **Positive** for **MUC1**, **e-cadherin** (**basolateral**), and **p120** (basolateral)
- **Prognostic markers: Positive** for **ER** and **PR**, and **50%** are **positive for HER2**

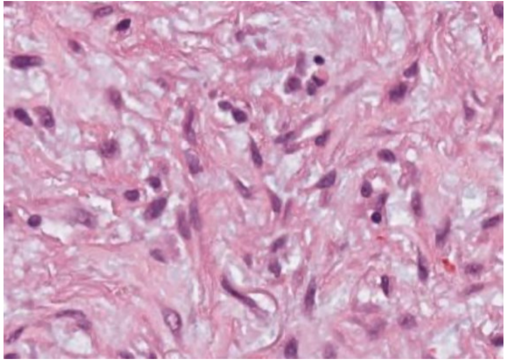
Low-grade adenosquamous carcinoma



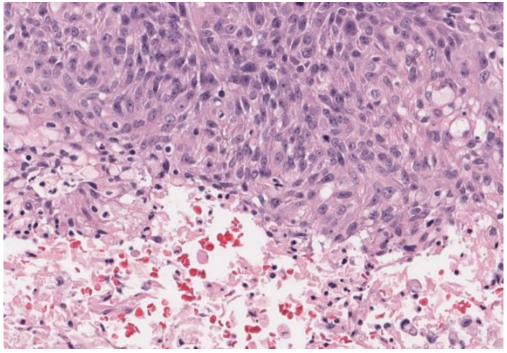
Fibromatosis-like metaplastic carcinoma



Spindle cell carcinoma



Squamous cell carcinoma



METAPLASTIC CARCINOMA

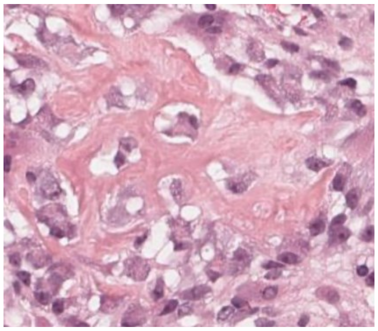
MORPHOLOGY

- **Invasive carcinoma** with a **wide spectrum of differentiation** of the epithelium towards squamous or mesenchymal-like elements
- **Several distinct patterns** (with some overlap, often mixed)
  - ➢ **Low-grade adenosquamous carcinoma** – Well-developed, rounded glands and tubules associated with solid squamous nests infiltrating through desmoplastic stroma; sometimes associated "cannon ball" lymphoid aggregates; associated with a **good prognosis**
  - ➢ **Fibromatosis-like metaplastic carcinoma** – Bland spindled cells with pale eosinophilic cytoplasm and slender nuclei with mild atypia (or may be plump and epithelioid) in stroma with variable collagen and often arranged in fascicles; associated with a **good prognosis**
  - ➢ **Spindle cell carcinoma** – Atypical spindle cells with a variety of architectural patterns (fascicles, herringbone) and have elongated to plump spindled cells with moderate to high-grade cytologic atypia; there is often associated inflammation; this category includes a spectrum of tumors from sarcomatoid SCC to myoepithelial carcinoma; associated with a **worse prognosis**
  - ➢ **Squamous cell carcinoma** – Pure squamous cell carcinoma and is often cystic; most important thing is to exclude a metastasis; associated with a **worse prognosis**
  - ➢ **Metaplastic carcinoma with heterologous mesenchymal differentiation** – Is essentially a carcinosarcoma and the heterologous elements may include chondroid, osseous, or rhabdoid components; epithelial and mesenchymal components can have variable atypia; extensive sampling is often necessary to find the epithelial component and exclude a primary sarcoma of the breast

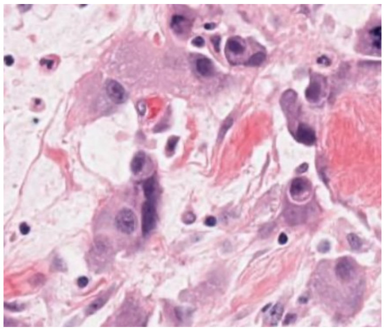
OTHER HIGH YIELD POINTS

- **Rare type** of cancer that **composes <1% of all breast cancers**
- Usually presents as a **large palpable mass**
- **Prognostic markers:** Negative for ER, PR, and HER2 (**triple negative)**
- IHC: **Positive for TRPS1**, **p63**, **HMWCKs**(CK5/6), **CKAE1/AE3**, **SOX10** (~50%); **negative for CK7**, **CD34**; variable SMA, CD10, desmin, and β-catenin
- **Molecular:** M**utations in TP53** (~65%), **PIK3CA** (~60%), **TERT promoter** (~45%) **PTEN** (~15%), NF1 (~!5%), PIK3R1 (~10%), and AKT (~5%), Wnt, and RB1

Path Presenter

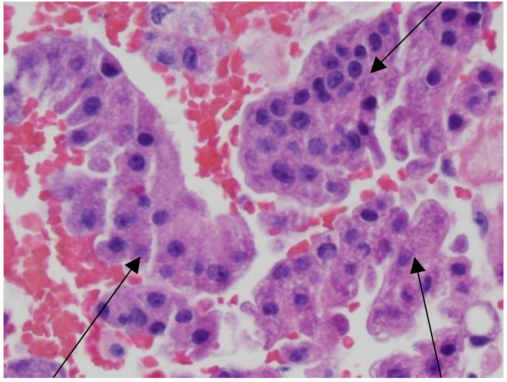


Osseous component

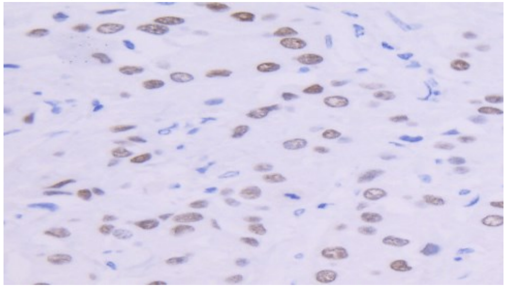


Rhabdoid component

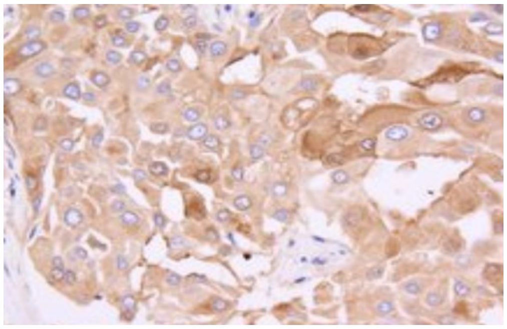
Apocrine carcinoma (Metastasis to bone)



Androgen receptor (AR)



GCDFP15



AR and GCDFP15 , image credits : Takashi Fujisawa M.D., Ph.D. (@Patholwalker)

INVASIVE APOCRINE CARCINOMA

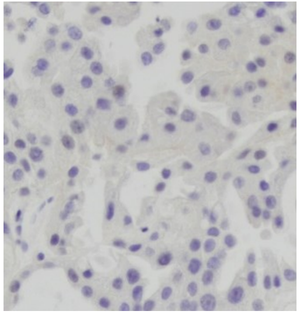
MORPHOLOGY

- The tumor cells have **large nuclei** with **prominent conspicuous nucleoli**, **vesicular chromatin**, and have **abundant granular eosinophilic cytoplasm**
- Must have **>90% of tumor cells must have** apocrine **morphology**
- May be arranged in **well-formed tubules**, **solid** or **sheet-like**, or **single cell** “**lobular**” **pattern**
- **Type A cells:** Intensely staining, abundant granular eosinophilic cytoplasm and round nuclei with prominent conspicuous nucleoli
- **Type B cells:** Abundant, finely vacuolated cytoplasm (resemble histiocytes) and have round nuclei with prominent conspicuous nucleoli

OTHER HIGH YIELD POINTS

- **Rare** breast carcinoma seen in older women
- **Favorable prognosis**
- IHC: **Positive** for **cytokeratins**, **AR**, **GCDFP15**; **negative** for **TRPS1, GATA3**
- **Special stains:** Intracytoplasmic granules are **PAS positive**
- **Prognostic markers:** Negative for ER, PR, HER2 (~50%) (**triple-negative**)
- **Molecular**: Mutations in **PIK3CA** (>80%), **TP53** (~30%), **PTEN** (~30%)
- **Electron microscopy**: **Prominent mitochondria** with occasional **abnormal cristae**; and membrane bound **vesicles** that are **400-600 nm** and have **dense secretory granules**
- **Cytogenetics:** Loss of heterozygosity of 17p13 (TP53), 3p25 (VHL), 16p13 (PKD1/TSC2), and 1p35-36 (NB), and abnormalities of 7q (encodes GCDFP15)

TRPS1 negative



GATA3 negative

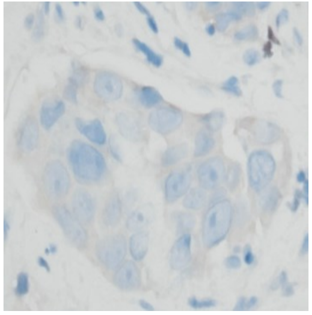
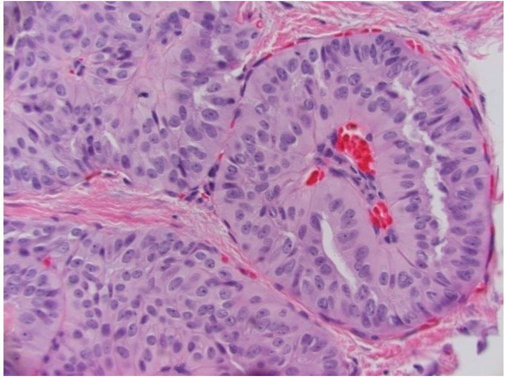


Image credits: Dr. Terrance Lynn, MD



Provided by Dr. Kimberly Heightchew, MD

TALL CELL CARCINOMA WITH REVERSE POLARITY

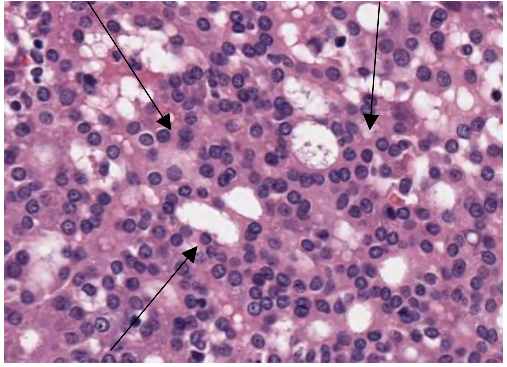
MORPHOLOGY

- **Tall columnar cells** with **reverse nuclear polarity** (nuclei at apical border)
- Nuclei are round to oval and have mild contour irregularities, conspicuous nucleoli, variable chromatin, and eosinophilic cytoplasm
- Tumor cells are arranged in **solid** and **solid papillary patterns**
- Scattered calcifications can be seen in the papillary areas

OTHER HIGH YIELD POINTS

- **Rare** and **indolent** invasive carcinoma that resembles papillary thyroid carcinoma but nuclei are not basally located
- IHC: **Positive** for **HMWCK** and **LMWCK** (CK5/6, CK7), and **calretinin**
- Prognostic markers: Negative for ER, PR, and HER2 **(triple negative)**
- **Molecular**: **IDH2 R172 hotspot mutation** (>80% of cases), **PIK3CA** (~67%)

INVASIVE CARCINOMA OF SALIVARY-GLAND TYPE



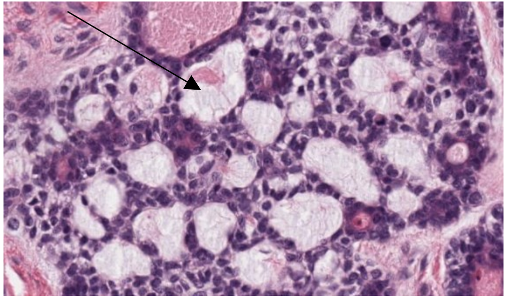
ACINIC CELL CARCINOMA

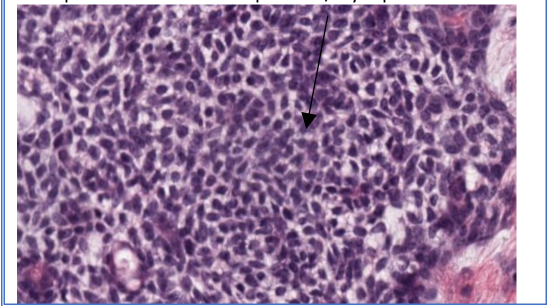
MORPHOLOGY

- Invasive carcinoma composed of tumor cells that have **centrally located**, **round nuclei**, **prominent** conspicuous **nucleoli**, and **finely granular pale eosinophilic** to **clear vacuolated cytoplasm**
- May have **dark staining granules** in cells which **may resemble Paneth cells**
- Often has a **microglandular formation**
- Frequently has **easily seen mitosis** scattered throughout

OTHER HIGH YIELD POINTS

- **Very rare** carcinoma of the breast with <20 known cases
- In the rare cases, many were **female in their 30s-40s**
- Grossly the tumor is **well-circumscribed** with a pink hemorrhagic cut surface
- IHC: **Positive for CK7**, E-cadherin, EMA; **negative for GCDFP15**, MUC2, SMA,
- **Prognostic markers:** Negative for ER, PR, and HER2 (**triple negative**)





ADENOID CYSTIC CARCINOMA

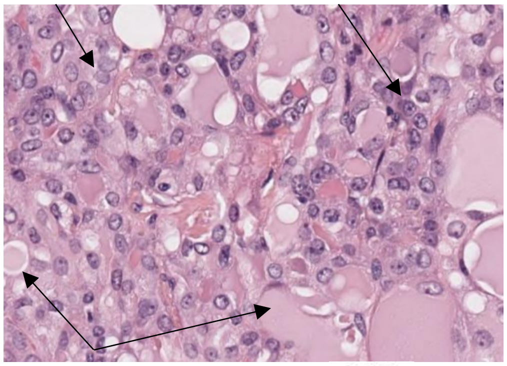
MORPHOLOGY

- Malignant **epithelial cells and myoepithelial cells** that are arranged in **tubules**, **cribriform**, and **solid patterns** with an associated **basophilic matrix** and **basement membrane material**

OTHER HIGH YIELD POINTS

- **Very rare** and majority occur in **middle-aged females**
- Presents as a **palpable lobulated** or **circumscribed mass below** the **nipple**
- **Prognosis is good**, >90% survival at 10 years
- **Distant metastasis is uncommon**; **solid-basaloid pattern** more **likely to metastasize and** has a **poorer prognosis** than classic pattern
- IHC: Epithelial cells are **positive** for **MYB**, **LMWCK**, **EMA**, CEA, and **CD117**, myoepithelial cells positive for p63, SMA, calponin, maspin, CK14, CK17
- **Prognostic markers**: Negative for ER, PR, and HER2 (**triple negative**)
- **Molecular**: **Translocation** of **t(6;9)(q22-23;p23-24)** resulting in a **MYB-NFIB fusion**
- Treatment is surgical with complete excision and negative margins

Path Presenter



Path Presenter

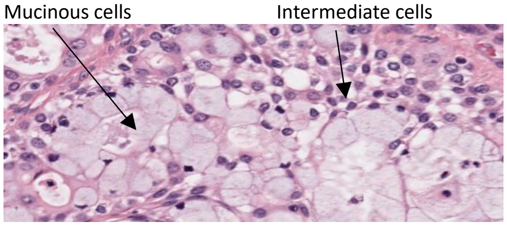
SECRETORY CARCINOMA

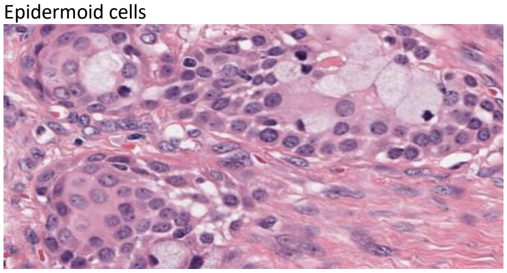
MORPHOLOGY

- Malignant **epithelial cells with uniformly round nuclei** with **no significant pleomorphism**, **small nucleoli**, **vacuolated eosinophilic cytoplasm** containing **secretory material**
- Lumina contains **dense eosinophilic secretions**
- May be in a **solid**, **tubular**, or **microcystic** pattern

OTHER HIGH YIELD POINTS

- Special stains: **Secretory material** is **PASD positive**
- IHC: **Positive** for **GATA3**, **S100**, **cytokeratins**, e-cadherin, **C-kit**, **Pan-TRK**, p63 and **negative** for **SOX10**, **MUC4**
- **Prognostic markers:** Negative for ER, PR, and HER2 (**triple negative**)
- **Molecular: Balanced translocation** of **t(12;15)(p13;q25) → ETV6-NTRK3**
- FISH: Break apart probes for ETV6





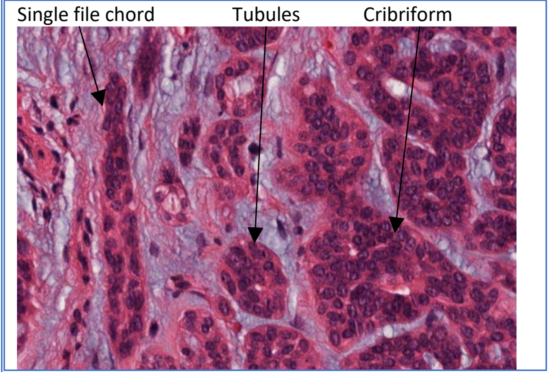
MUCOEPIDERMOID CARCINOMA

MORPHOLOGY

- Malignant epithelial carcinoma that is **composed of mucinous cells**, **intermediate cells**, and **epidermoid (squamous) cells**
- The tumor cells are usually arranged in a **solid or cystic pattern**
- **Mucinous** and **intermediate cells** are most often **seen lining the cystic spaces or** within the **epidermoid areas**
- The background **stroma may be sclerotic** and there may be **foci of mucin**
- **High-grade** tumors often have **scattered mitosis**, **necrosis**, and **pleomorphism**

OTHER HIGH YIELD POINTS

- **Very rare** carcinoma of the breast and resembles salivary counterpart
- **Very good prognosis if low-grade**
- IHC: **Positive** for **HMWCK**, **p63, EMA**, CEA
- **Prognostic markers**: Negative for ER, PR, and HER2 (**triple negative**)
- **Molecular**: **MAML2 fusions**; MAML2 is located on **chromosome 11q**
  - ➢ **Most common** is **t(11;19)(q14-21;p12-13) → CRTS1(MECT1)-MAML2**
- FISH: Break apart probe for MAML2



POLYMORPHOUS ADENOCARCINOMA

MORPHOLOGY

- Monotonous **neoplastic cells** with **round to ovoid nuclei**, **vesicular chromatin**, and **eosinophilic cytoplasm**
- Tumor cells are **arranged in** a variety of patterns including **large nests**, **tubules**, **trabeculae**, **cribriform**, **alveolar**, or **single file chord patterns**
- **Mitosis** are **easily seen** and usually there is **no necrosis**

OTHER HIGH YIELD POINTS

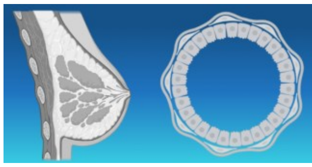
- **Very rare** carcinoma of the breast
- IHC: **Positive for CK7 (weak)**, **BCL2** (strong), **CK5/6**, **GFAP** (focal); negative for EMA and CD117
- **Prognostic markers:** Negative for ER, PR, and HER2 (**triple negative**)

BRCA & SYNDROMIC-RELATED BREAST CANCERS

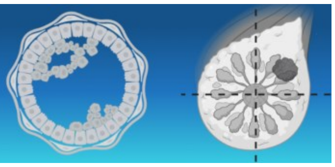
BREAST CANCER GENE 1 AND 2 (BRCA1, BRCA2)

- BRCA-genes are **tumor suppressors** involved in the **homologous recombination repair pathway**
- **Highest risk** is **for breast** and **ovarian cancer**
- Accounts for nearly **3.5% of all breast cancers**; more common in certain populations, like **Ashkenazi Jews**
- **Treatment:** patients may opt for **prophylactic bilateral mastectomy** and **salpingo-oophorectomy** before **40 years of age**
  - ➢ Must submit entire fallopian tube and ovary looking for **serous tubal intraepithelial carcinoma (STIC) lesions**
- Carcinomas can be **treated** with **poly-ADP ribose polymerase (PARP) inhibitors**
  - ➢ When a single stranded DNA break occurs, PARP binds to the DNA, then undergoes confirmational change and begins synthesis of polymeric adenosine diphosphate ribose, which acts as a signal for other repair enzymes
  - ➢ Addition of **PARP inhibitor in conjunction with BRCA mutations**, the **cancer cells cannot repair and DNA** strand breaks

Characteristic	**BRCA1**	**BRCA2**
Risk of breast cancer	40-90%	45-85%
Risk of ovarian /fallopian tube high grade serous carcinoma	40-50%	10-20%
Male breast cancer risk	Lower	Higher
Other cancer risk	Possibly pancreatic and colon	Pancreatic cancer, prostate cancer
Morphology	Circumscribed growth pattern with pushing borders, lymphocytic infiltrate, high-grade	Variable morphology and grade
Molecular cancer type	Basal-like(triple-negative)	Luminal A (ER/PR+; HER2-)



2. BREAST PATHOLOGY



LI FRAUMENI SYNDROME 1 (TP53-ASSOCIATED)

- Inheritance pattern: **Autosomal dominant**
- Gene affected: **TP53** (prominent tumor suppressor gene)
- Defect causes early onset of a **broad spectrum of cancers**, of which the **most common is breast (>90% lifetime risk)** but also soft tissue sarcomas, osteosarcomas, brain (esp. choroid plexus carcinoma), adrenal cortical carcinoma, acute leukemia, melanoma, Wilms' tumor, gastroesophageal, colorectal, pancreas, and gonadal cancers

LI FRAUMENI SYNDROME 2 (TP53-UNASSOCIATED; CHK2-ASSOCIATED)

- **Heterozygous germline mutation** with **low to moderate penetrance**
- Gene affected: **CHEK2 (tumor suppressor gene)**
- Mutation: **CHEK2 1100delC**
- Risk of cancer: There is a **30% lifetime risk of breast cancer** and there is an **increased risk of** a variety of **other cancers**
- Normal gene function: **CHEK2** is **activated** by **double strand DNA breaks** (upstream of TP53 and BRCA1)
  - **Mutations disrupt DNA repair** which allows for more errors and leads to carcinogenesis.

PEUTZ-JEGHERS SYNDROME

- Inheritance pattern: **Autosomal dominant**
- Gene affected: **STK11 (tumor suppressor gene)**
- Characteristic **hamartomatous polyps** in **>95% of patients** (often small bowel), **mucocutaneous melanin pigmentation**
- **Increased risk of many cancers** including **breast**, colon, stomach, pancreas, ovary (SCATs), etc.

CDH1-ASSOCIATED DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME

- Inheritance pattern: **Autosomal dominant**
- Gene affected: **CDH1 inactivating mutations** (cell adhesion and tumor suppression gene) on **chromosome 16q22**
- **Lifetime risk of cancer** in carrier individuals is **>80%**; **Nearly 60% of all female carriers develop lobular carcinoma** of the breast
- Cancers present as a characteristic **single file**, **discohesive**, **signet ring cells** and **pagetoid spread**
- **Cancers in the stomach** are **signet ring cell adenocarcinoma** and usually **affects the submucosa** and is **not seen endoscopically**
- **Somatic mutations in CDH1 are also seen** in individuals **with sporadic** lobular carcinoma and diffuse gastric cancer

ATAXIA-TELANGIECTASIA

- Inheritance pattern: **Autosomal recessive**
- Gene affected: **ATM gene** (tumor suppressor that phosphorylates p53 and BRCA1 when dsDNA breaks occur)
- **Carriers** (heterozygous: one normal and one mutant allele) **have an increased risk of breast cancer at a young age** but **do not have syndrome** because they maintain a normal copy of the gene
- Patients present with **progressive cerebellar ataxia**, **oculocutaneous telangiectasia**, **variable immunodeficiency**, sterility, and **recurrent sinopulmonary infections**
- **High risk of malignancy** and patients are very **sensitive to ionizing radiation** (including X-rays for medical purposes)

COWDEN SYNDROME (MULTIPLE HAMARTOMA SYNDROME)

- Inheritance pattern: **Autosomal dominant**
- Gene affected: **PTEN gene** (tumor suppressor gene)
- Affected patients usually have **macrocephaly**, **facial trichilemmomas**, **acral keratoses**, **papillomatous papules**, **lipomas**, esophageal **glycogen acanthosis**, multiple **stomach polyps resembling hyperplastic polyps**, colon polyps with cystically dilated glands, **colon with adipocytes in lamina propria** (unique), and **ganglioneuromatous polyps**
- Mutation **predisposes patients to breast cancer** (**highest risk**), **multiple hamartomas** (mouth, GI tract), **follicular thyroid carcinoma** (most often), and **endometrial c**ancer
- Other PTEN syndromes include: **Bannayan-Riley-SMITH-Myhre-Ruvalcaba syndrome**, and **Lhermitte-Duclos disease**

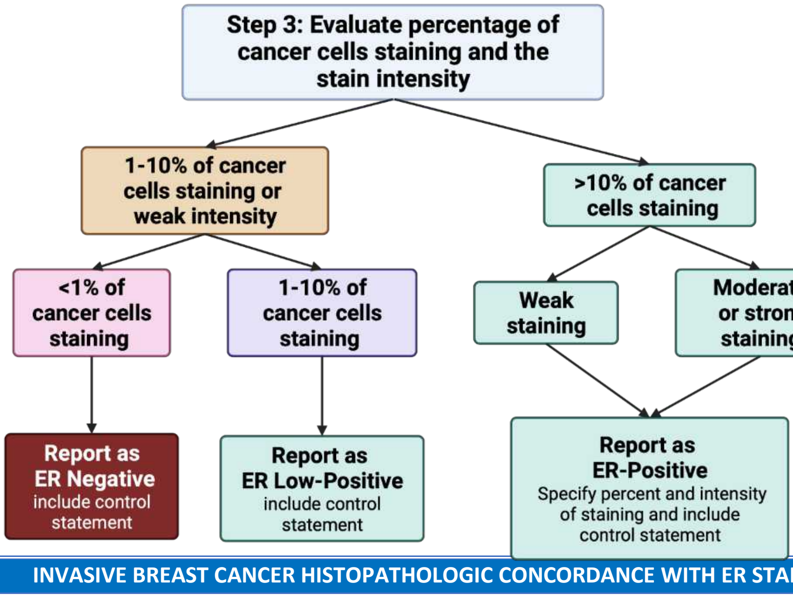
PROGNOSTIC MARKER TESTING

ESTROGEN RECEPTOR (ER)

- **Step 1: Preanalytical quality control check and appropriateness of prognostic marker testing**
  - Is the **cold-ischemia time** (time from tissue removed to placement in fixative) documented?
    - Cold ischemia time is **preferred to be less than 1 hour** as **prolongation results in antigen degradation**
  - **What fixative is used**? Do these meet the latest ASCO/CAP guidelines?
  - Is the **fixation time at least 6 hours or more**? Does it meet the latest ASCO/CAP guidelines?
  - Has the **tissue been altered** in any way that could **affect immunogenicity** (**decalcification**)?

    - **ER is degraded in acidic fixatives**; such fixatives include Bouin's and B-5
    - **Buffered formalin** is the recommended and should have a **pH between 7.0 and 7.4**
    - **Prolonged fixation** can also **result** in **loss of immunogenicity**
    - Each lab should have their validated acceptable fixation time window
  - **If the information is not available**, then a **statement regarding the absence of certain information** should be **added to report** and results should be **interpreted with caution**

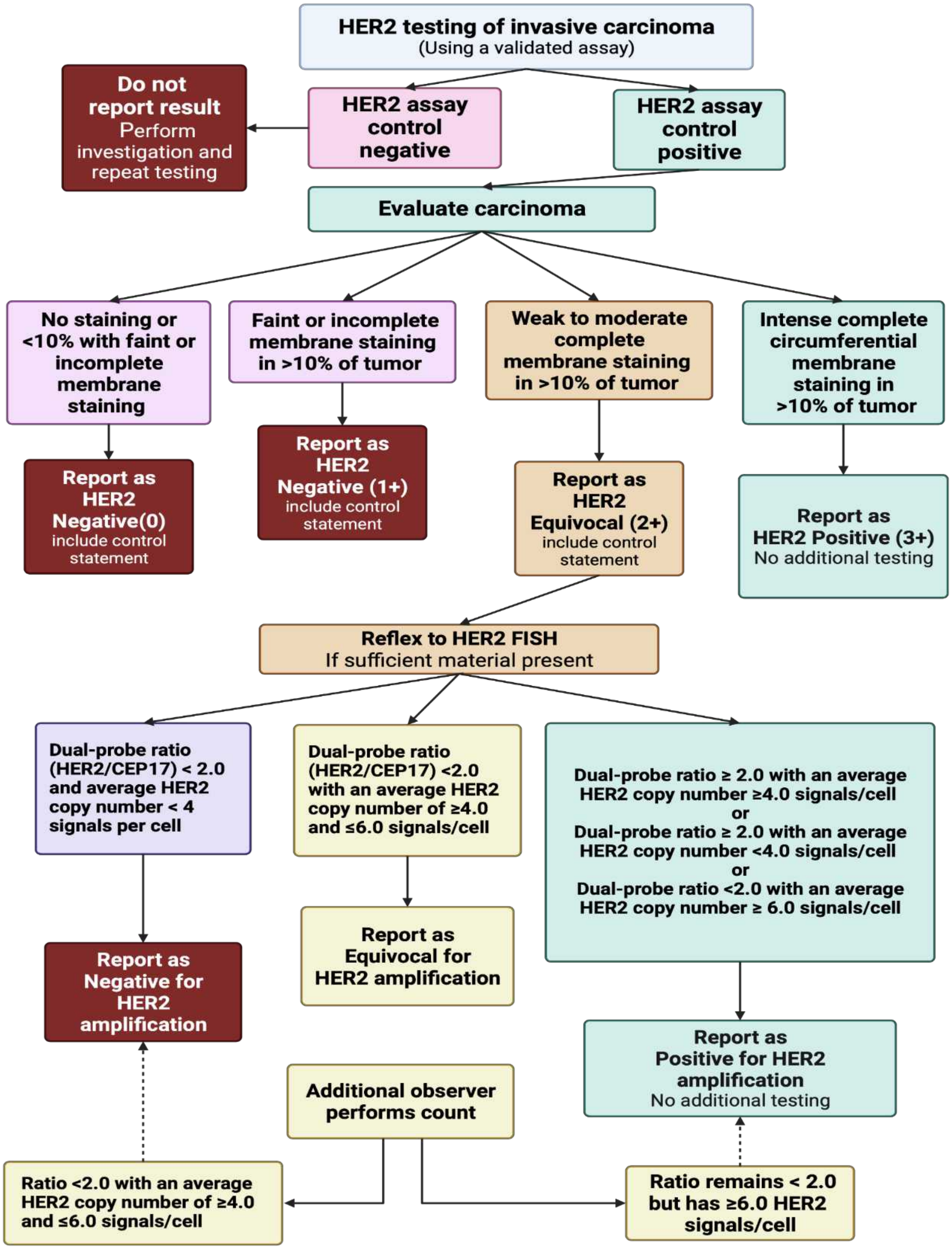
- **Step 2: Analytical quality control check**
  - Is the **sample adequate for testing** (sufficient tumor for testing)?
  - Are the **correct antibody clones** being used? Are they FDA cleared or are they a laboratory developed test?
  - What is the **status of the internal control** (normal epithelial cells that are positive)?
    - If there is no normal internal control, this should be mentioned in the report
  - What is the **status of the external control** (cancer cell lines that are positive, etc)?
    - If this is negative, an investigation should occur and repeat staining (if enough tissue exists)
    - If positive control failed, a negative result cannot be confirmed


Step 3: Evaluate percentage of cancer cells staining and the stain intensity
1-10% of cancer cells staining or weak intensity
>10% of cancer cells staining
<1% of cancer cells staining
1-10% of cancer cells staining
Weak staining
Moderate or strong staining
Report as ER Negative include control statement
Report as ER Low-Positive include control statement
Report as ER-Positive Specify percent and intensity of staining and include control statement

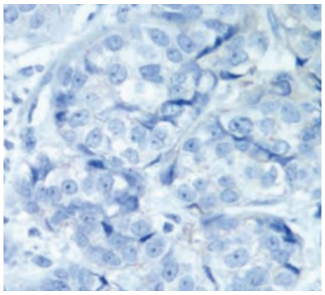
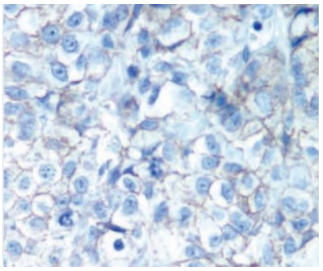
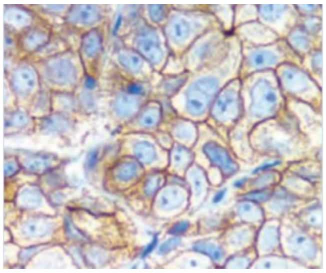
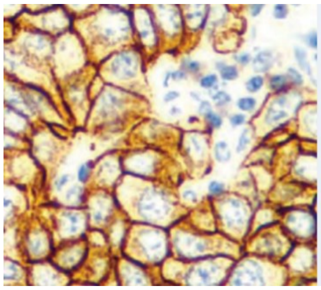
INVASIVE BREAST CANCER HISTOPATHOLOGIC CONCORDANCE WITH ER STAINING	
Highly unusual ER-negative results	**Highly unusual ER positive results**
Low-grade invasive carcinomas of no special type	Metaplastic carcinomas of all subtypes
Lobular carcinoma (classic type)	Salivary gland-like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Invasive apocrine carcinoma

- **Step 4: Post-analytic control check prior to reporting results**
  - If a **result** is considered **highly unusual/discordant**, **additional steps should be taken prior** to report sign-out
  - Perform a **review of the preanalytical** and **analytic testing factors**
  - Check the **accuracy of the histologic type and grade**, if matches, proceed to an **independent, second review**
  - Perform an **independent second review** (by another pathologist) and **repeating testing**
  - If all **results appear valid** on independent second review and repeat testing matches, the **result can be reported**
    - Add a comment noting that the findings are highly unusual, and repeat testing was concordant, document second pathologist reviewed results, and add that testing of additional samples may be of value to confirm the findings

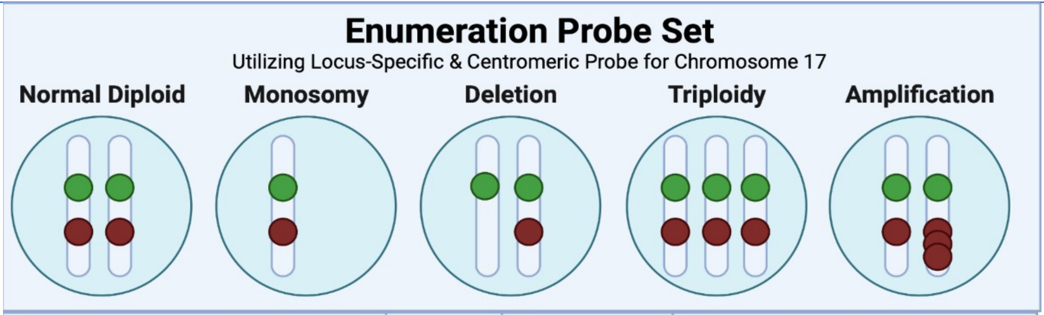
HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)

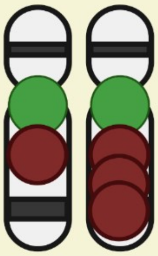
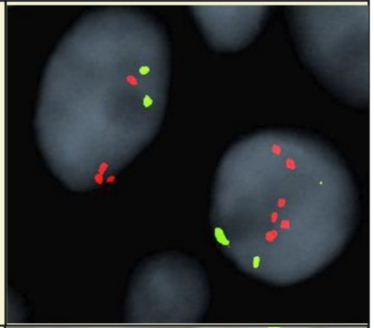
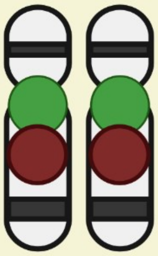
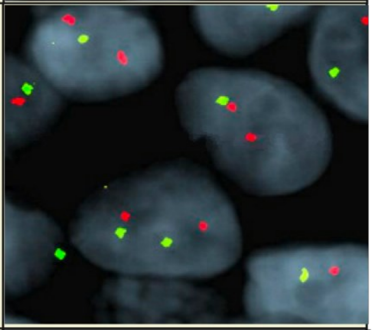
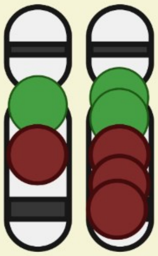
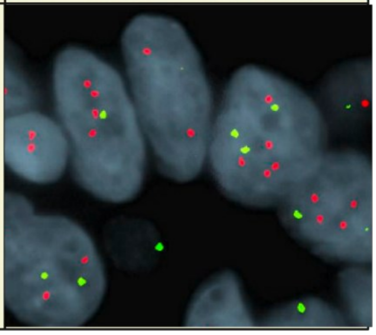

HER2 testing of invasive carcinoma
(Using a validated assay)
HER2 assay control negative
Do not report result
Perform investigation and repeat testing
HER2 assay control positive
Evaluate carcinoma
No staining or <10% with faint or incomplete membrane staining
Faint or incomplete membrane staining in >10% of tumor
Weak to moderate complete membrane staining in >10% of tumor
Intense complete circumferential membrane staining in >10% of tumor
Report as HER2 Negative(0)
include control statement
Report as HER2 Negative (1+)
include control statement
Report as HER2 Equivocal (2+)
include control statement
Report as HER2 Positive (3+)
No additional testing
Reflex to HER2 FISH
If sufficient material present
Dual-probe ratio (HER2/CEP17) < 2.0 and average HER2 copy number < 4 signals per cell
Dual-probe ratio (HER2/CEP17) <2.0 with an average HER2 copy number of ≥4.0 and ≤6.0 signals/cell
Dual-probe ratio ≥ 2.0 with an average HER2 copy number ≥4.0 signals/cell
or
Dual-probe ratio ≥ 2.0 with an average HER2 copy number <4.0 signals/cell
or
Dual-probe ratio <2.0 with an average HER2 copy number ≥ 6.0 signals/cell
Report as Negative for HER2 amplification
Report as Equivocal for HER2 amplification
Report as Positive for HER2 amplification
No additional testing
Additional observer performs count
Ratio <2.0 with an average HER2 copy number of ≥4.0 and ≤6.0 signals/cell
Ratio remains < 2.0 but has ≥6.0 HER2 signals/cell

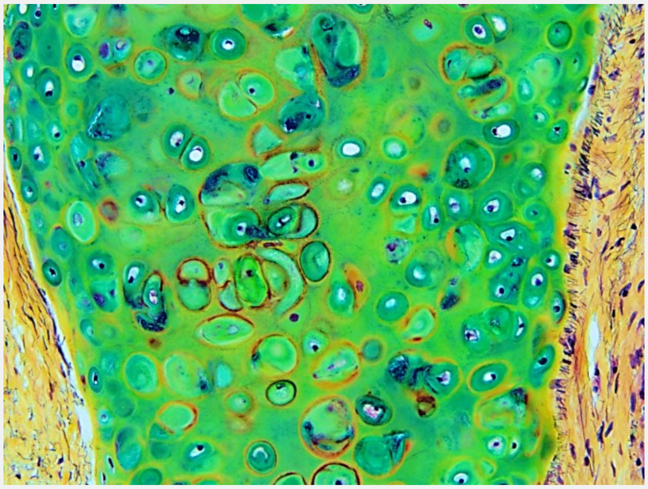
IMMUNOHISTOCHEMISTRY GRADING OF HER2 IN INVASIVE CARCINOMA OF THE BREAST

Score	Interpretation	Staining pattern	Thickness	IHC Image
0	**Negative**	**No staining** is observed, **or membrane staining** is observed in **<10% of tumor** cells	Essentially **nothing**, like an eraser	
1+	**Negative**	A **faint/barely perceptible membrane staining** is detected **in >10% of tumor** cells; the cells exhibit incomplete membrane staining	Slight **pencil tracing**	
2+	**Equivocal (order FISH)**	A **weak to moderate complete, circumferential membrane staining** is observed in **>10 of tumor cells**	**Ballpoint** pen	
3+	**Positive**	A **strong complete membrane staining** is observed in **>10% of tumor** cells	**Sharpie** marker	

HER2 FLUORESCENCE IN SITU HYBRIDIZATION IN INVASIVE BREAST CANCER


Enumeration Probe Set
Utilizing Locus-Specific & Centromeric Probe for Chromosome 17
Normal Diploid
Monosomy
Deletion
Triploidy
Amplification

Chromosome Appearance	HER2/ CEP17 Ratio	HER2 signals per cell	FISH Appearance
Classic Amplified 	≥ 2.0	≥ 6.0	
Classic Non-amplified 	< 2.0	<4.0	
Equivocal 	< 2.0	4.0-6.0	

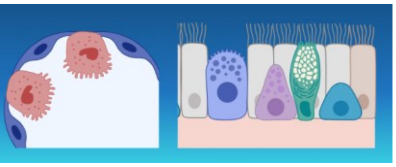


Movat Pentachrome stain in Bronchial cartilage.
Image courtesy: Sanjay Mukhopadhyay, MD

CHAPTER 3: PULMONARY PATHOLOGY

Jian Li, MD
Jared T. Ahrendsen, MD, PhD
Akanksha Gupta, MD

3. PULMONARY PATHOLOGY



HISTOLOGIC FINDINGS OF IDIOPATHIC INTERSTITIAL PNEUMONIA

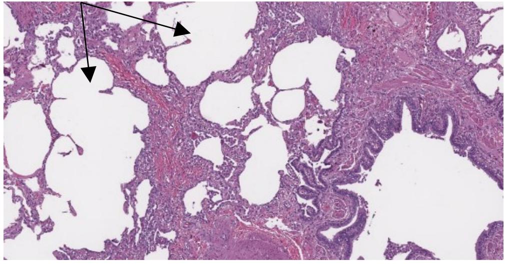
	Nonspecific Interstitial Pneumonia (NSIP)	Usual Interstitial Pneumonia (UIP)	Desquamative Interstitial Pneumonia (DIP)	Acute Interstitial Pneumonia (AIP)	Lymphoid Interstitial Pneumonia (LIP)	Cryptogenic Organizing Pneumonia (COP)
Temporal appearance	Uniform	**Varied**	Uniform	Uniform	Uniform	Uniform
Interstitial inflammation	**Prominent**	Scant	Scant	Scant	**Prominent**	Scant
Interstitial collagen	Variable, diffuse	Patchy	Variable, diffuse	No	Some cases	No
Interstitial fibrosis	Rare, diffuse	No	No	**Yes, diffuse**	No	No
OP pattern	Occasional, focal	Occasional, focal	No	Occasional, focal	No	**Prominent**
Fibroblastic foci	Occasional, focal	**Typical**	No	No	No	No
Honeycombing	Rare	**Typical**	No	No	Occasional	No
Intra-alveolar macrophages	Occasional, patchy	Occasional, focal	**Yes, diffuse**	No	Occasional, patchy	No
Hyalin membranes	No	No	No	**Yes**	No	No
Granulomas	No	No	No	No	No	No

DISEASES WITH BRONCHOGENIC GRANULOMAS

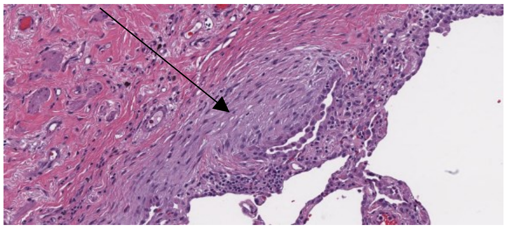
Aspiration	Degenerating **food particles**; history of stroke, epilepsy, GERD, dementia, etc.
Sarcoidosis	Tightly formed, non-necrotizing granulomas; also, along pleura and septa
Infection	Positive cultures or special stains
Hypersensitivity Pneumonitis	**Peribronchiolar** inflammation, chronic bronchiolitis, peribronchiolar metaplasia (“Lambertosis”), relevant exposure history (birds, molds, occupational, etc.)
Allergic Bronchopulmonary Aspergillosis (ABPA)	Allergic mucin (Charcot-Leyden crystals and eosinophils), eosinophilic pneumonia, asthma/asthmatic airway changes, rare fungal elements
Granulomatosis with Polyangiitis	**Vasculitis**, capillaritis, diffuse alveolar hemorrhage, positive ANCA, relevant history/clinical findings
Middle Lobe Syndrome	Limited to the middle lobe
Rheumatoid Arthritis	Rheumatoid nodules, relevant clinical history (arthritis, +RF, etc.)

MEDICAL LUNG DISEASE - FIBROSIS

Distorted cystic spaces (honeycombing)



Fibroblastic focus



USUAL INTERSTITIAL PNEUMONIA(UIP)/IDIOPATHIC PULMONARY FIBROSIS

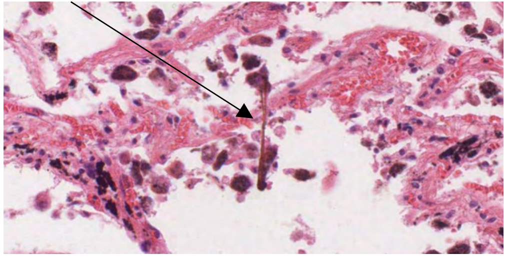
MORPHOLOGY

- **Temporally and spatially heterogeneous**: The disease is patchy, with some advanced areas and other early areas
- Minimal inflammation
- **Fibroblastic foci**: Immature fibroblastic areas
- **Honeycombing**: Architecturally distorted cystic spaces with respiratory epithelium and surrounding fibrosis
- Fibrosis is worst in **lower lobes** adjacent to pleura and septa (cannot diagnose on transbronchial biopsy)

OTHER HIGH YIELD POINTS

- **UIP is a histologic pattern**; it can be seen with connective tissue diseases, chronic hypersensitivity pneumonitis, drug reactions, or idiopathic
- Typical presentation: Older male with gradually increasing shortness of breath; eventually fatal

Path Presenter



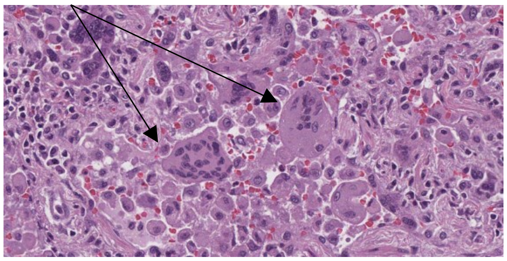
ASBESTOSIS

MORPHOLOGY

- **Interstitial fibrosis** with minimal associated inflammation; fibroblastic foci absent
- **Asbestos bodies**: Dumbbell-shaped iron deposits
- **Pleural plaques** visible grossly

OTHER HIGH YIELD POINTS

- Caused by **inhalation of silicate mineral fibers** (not just asbestos)
- Often due to **occupational** exposure (miner, construction, shipyards, etc.)
- Increased risk of lung cancer and mesothelioma



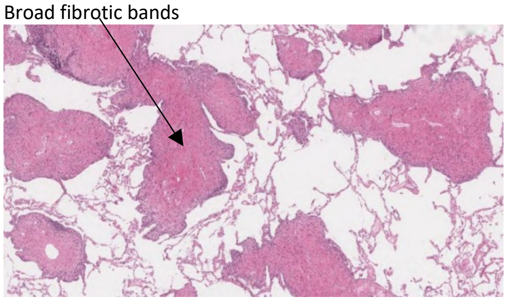
HARD METAL PNEUMOCONIOSIS

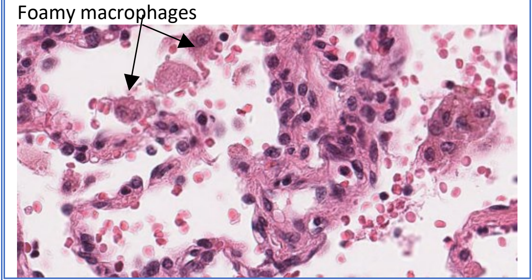
MORPHOLOGY

- **Giant cell interstitial pneumonia**
- Intra-alveolar **giant cells** and **fibrosis** with variable inflammation
- Frequent emperipolesis

OTHER HIGH YIELD POINTS

- Caused by **inhalation of hard metals**, usually **cobalt**
- Other metals: tungsten, titanium
- Occupational exposure: manufacturing, drilling, sawing





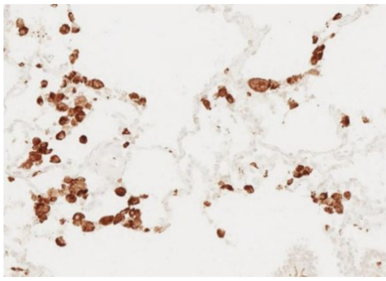
ERDHEIM-CHESTER DISEASE

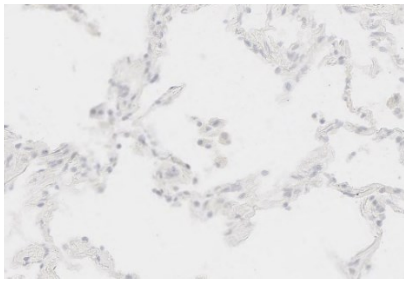
MORPHOLOGY

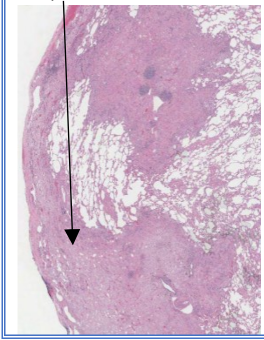
- **Broad fibrotic bands** with intermixed foamy to pink **histiocytes**
- Scattered **touton-type giant cells**

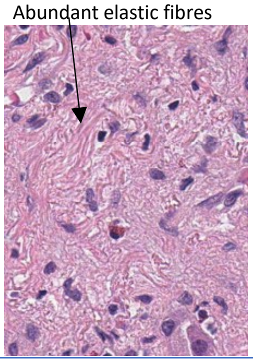
OTHER HIGH YIELD POINTS

- **Multisystem histiocytosis** that can involve any organ (frequently involves long bones)
- IHC: Macrophages stain with CD68, Factor XIIIa; (+/-) S100
- Some show BRAF V600E gene mutations


CD68


S100





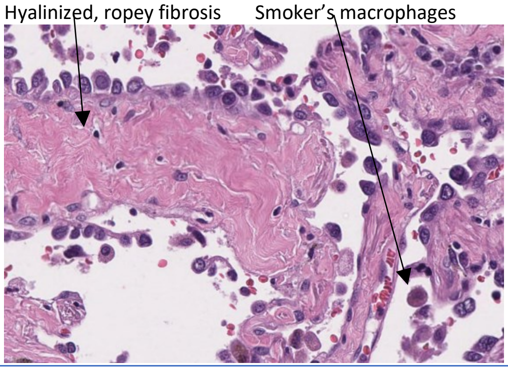
PLEUROPARENCHYMAL FIBROELASTOSIS

MORPHOLOGY

- Early: **Upper lobe predominant subpleural fibrosis with abundant elastic fibers** (highlight with elastin stain, which are smaller and more lightly colored than collagen)
- Minimal to no inflammation, granulomas, or fibroblastic foci

OTHER HIGH YIELD POINTS

- Rare, diffuse interstitial disease
- Idiopathic or associated with stem cell transplant, medications, exposure, etc.
- If localized apical mass lesion, consider “apical cap”



Hyalinized, ropey fibrosis

Smoker's macrophages

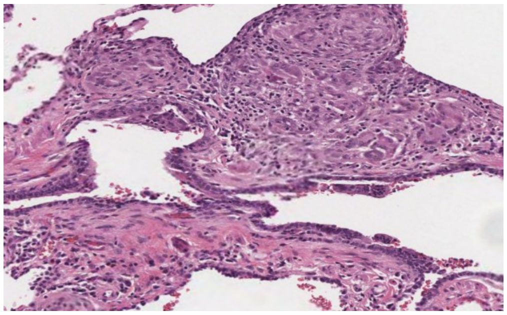
OTHER FIBROTIC DISEASES

- **SMOKING-RELATED INTERSTITIAL FIBROSIS (SRIF)**
    - **Hyalinized, ropey fibrosis**; respiratory bronchiolitis (smoker's macrophages); emphysema
- **CHRONIC HYPERSENSITIVTY PNEUMONITIS**
    - Cellular infiltrates, esp. near airways
    - Loosely formed, **non-necrotizing granulomas** and/or giant cells
- **CHRONIC NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)**
    - NSIP (see below) with homogenous fibrosis

OTHER HIGH YIELD POINTS

- Many diseases can become fibrosis-predominant when more advanced, so look for clues to other etiologies

MEDICAL LUNG DISEASE - CELLULAR INTERSTITIAL INFILTRATES



Peribronchiolar granulomas/giant cells, chronic inflammation, fibrosis

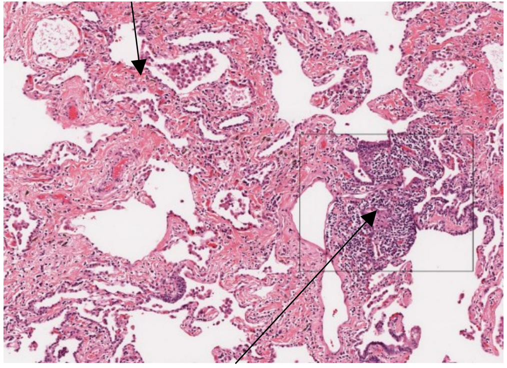
HYPERSENSITIVITY PNEUMONITIS (HP)

MORPHOLOGY

- **Airway-centric inflammation** with **peribronchiolar** granulomas/giant cells, peribronchiolar interstitial chronic inflammation, and chronic bronchiolitis
- Can see peribronchiolar metaplasia, organizing pneumonia, cholesterol clefts, fibrosis (chronic HP)

OTHER HIGH YIELD POINTS

- Due to **inhalation of small organic or chemical antigens** that stimulate an immune response
- Common antigens: Birds ("Pigeon fancier's lung"), molds ("Farmer's lung"), wood dust, certain industrial chemicals
- Often delayed diagnosis and insidious onset of dyspnea



Homogeneous thickening of alveolar septa

Chronic inflammatory infiltrates

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

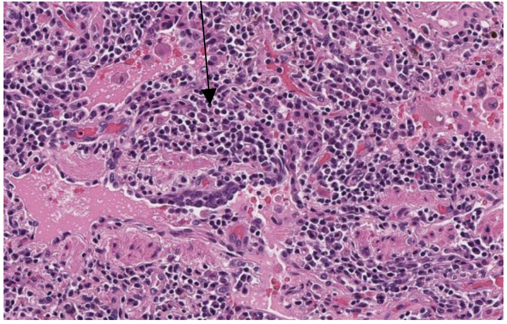
MORPHOLOGY

- A pattern of inflammation with **homogeneous, diffuse thickening** of alveolar septa by **chronic inflammatory infiltrates**
- Can see associated homogenous **fibrosis** (chronic NSIP)

OTHER HIGH YIELD POINTS

- Most commonly due to connective tissue disease (**prominent lymphoid follicles** ± geminal centers, pleuritis)
- It can also be idiopathic, medication-related, hypersensitivity pneumonitis
- Better prognosis than UIP/IPF

Path Presenter



Dense interstitial lymphoplasmacytic infiltrate

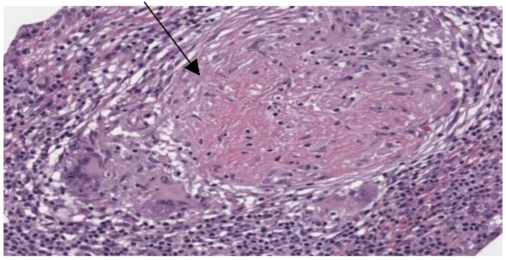
LYMPHOID INTERSTITIAL PNEUMONIA (LIP)

MORPHOLOGY

- Diffuse, dense, interstitial **lymphoplasmacytic infiltrate**
- Predominantly polymorphous **T cells**

OTHER HIGH YIELD POINTS

- Rare, idiopathic
- Must exclude other conditions, including lymphoma (esp. MALT lymphoma), autoimmune disease, HIV/AIDS, immunodeficient state (e.g., CVID)
- If numerous large lymphoid follicles surrounding airways, consider "follicular bronchiolitis"



HOT TUB LUNG

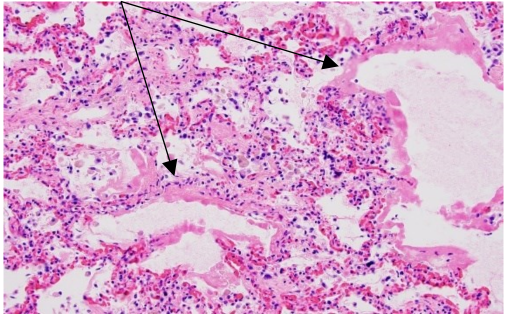
MORPHOLOGY

- Similar appearance to hypersensitivity pneumonitis (**peribronchiolar** chronic inflammation)
- **More prominent and better-formed granulomas**, which can be necrotizing

OTHER HIGH YIELD POINTS

- Hypersensitivity pneumonia-like reaction to **mycobacterium avium complex**, which is common in water (esp. indoor hot tubs, saunas, swimming pools)

MEDICAL LUNG DISEASE - ALVEOLAR FILLING PATTERN



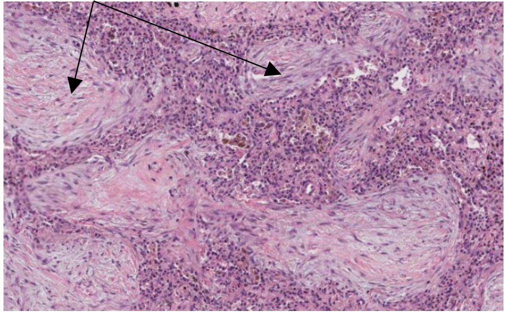
DIFFUSE ALVEOLAR DAMAGE (DAD)

MORPHOLOGY

- **Hyaline membranes**: Due to endothelial/epithelial injury causing leakage of serum proteins
- May also see necrosis and acute inflammation (esp. with infection)

OTHER HIGH YIELD POINTS

- Histologic manifestation of **acute respiratory distress syndrome (ARDS)**: Bilateral diffuse pulmonary infiltrates, often requiring ventilation
- Can be seen in a variety of settings (**common pathologic endpoint),** including infection, sepsis, drug reactions, toxins, and shock
- If idiopathic → "Acute Interstitial Pneumonia" (AIP)



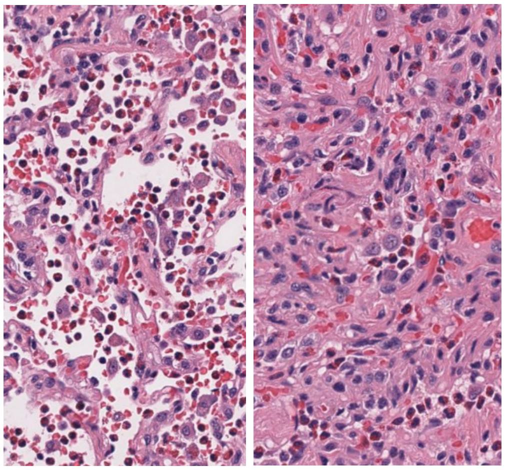
ORGANIZING PNEUMONIA

MORPHOLOGY

- Accumulation of **immature myxoid material** and fibroblasts within airspaces
- Can see **fibroblastic plugs**/polyps (Masson bodies) in airspaces
- Intact alveolar septa

OTHER HIGH YIELD POINTS

- Nonspecific pattern of lung injury/repair
- Can be seen after infection, injury, aspiration, connective tissue disease
- Often resolves after removing inciting agent
- If idiopathic → "Cryptogenic Organizing Pneumonia" (COP)



EOSINOPHILIC PNEUMONIA

MORPHOLOGY

- **Acute: diffuse alveolar damage** with the addition of **eosinophil-rich inflammation**; peripheral eosinophilia; eosinophils on bronchoalveolar lavage
- **Chronic:** intra-alveolar collections of eosinophils, macrophages, and edema

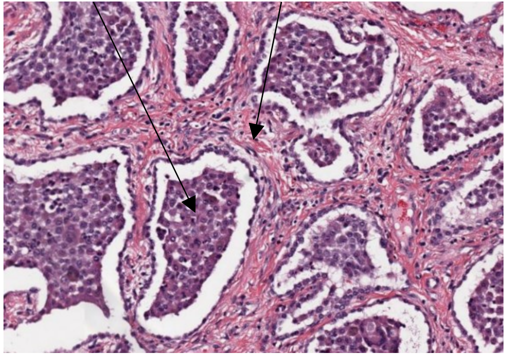
OTHER HIGH YIELD POINTS

- **Acute** eosinophilic pneumonia presents with fever and dyspnea of <1 month duration
    - DDX: Infection (parasites), medications, cigarettes, pneumothorax, idiopathic
- **Chronic** eosinophilic pneumonia presents with insidious onset; relapsing; responds to steroids
    - DDX: When idiopathic, often associated with asthma, medications, allergies

Path Presenter

3. PULMONARY PATHOLOGY

Smoker's macrophages and adjacent fibrosis



DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP) / RESPIRATORY BRONCHIOLITIS INTERSTITIAL LUNG DISEASE (RB-ILD)

MORPHOLOGY

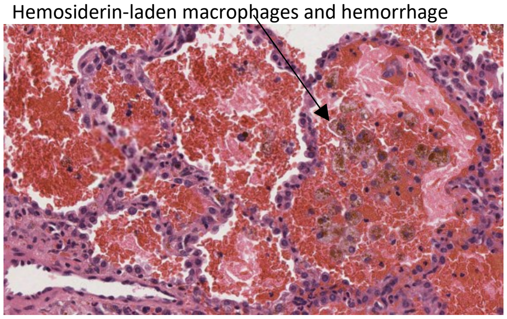
- DIP: **Filling of alveoli by pigmented macrophages**, often associated with fibrosis and mild chronic inflammation, homogeneous involvement
- RB-ILD: **Pigmented "smoker's" macrophages** in respiratory bronchioles and adjacent alveoli (not homogeneous like DIP)

OTHER HIGH YIELD POINTS

- Need clinical symptoms/findings to label RB-ILD as **ILD**
- Spectrum of disease highly associated with **smoking**

Path Presenter

Hemosiderin-laden macrophages and hemorrhage



ALVEOLAR HEMORRHAGE

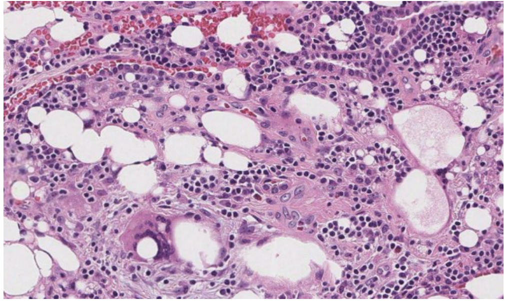
MORPHOLOGY

- **Hemosiderin-laden macrophages** and **fresh blood** in alveoli

OTHER HIGH YIELD POINTS

- Can be **secondary** to trauma, cardiac disease, vascular disease, medications
- **Diffuse alveolar hemorrhage** is often a result of vasculitis/capillaritis
- **Anti-GBM disease (Goodpasture syndrome)**: Autoantibodies to collagen IV in basement membrane; impacts capillaries in kidneys (crescentic glomerulonephritis) and lungs (hemorrhage)

Lipid-rich material in alveolar spaces



LIPOID PNEUMONIA

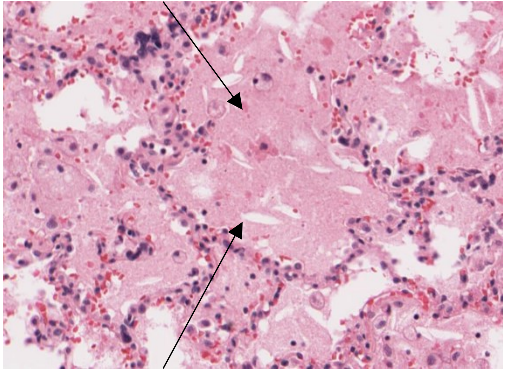
MORPHOLOGY

- **Lipid-rich material** and **inflammatory cells** filling alveolar spaces

OTHER HIGH YIELD POINTS

- **Endogenous/post-obstructive**: Proximal airway obstruction with an inability to clear secretions causes accumulation of **finely vacuolated macrophages** in distal airways
- **Exogenous/aspiration**: Aspiration of lipid-rich material (mineral oil) with accumulation of multinucleated giant cells containing **large lipid vacuoles**

Eosinophilic proteinaceous material in the alveoli



Cholesterol clefts

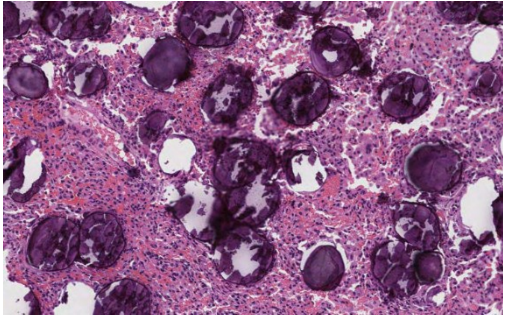
ALVEOLAR PROTEINOSIS

MORPHOLOGY

- Filling of alveoli by **amorphous eosinophilic, PASD(+) proteinaceous material**
- Occasional crystals and cholesterol **clefts**
- Resembles proteinaceous edema fluid (PAS-negative)

OTHER HIGH YIELD POINTS

- **"Crazy paving"** appearance on CT
- Three forms:
  - **Congenital**: Mutations of genes encoding surfactant or GM-CSF
  - **Primary**: Autoantibodies against GM-CSF causing abnormal macrophage function and accumulation of proteinaceous material
  - **Secondary**: Stem cell transplantation, solid organ transplantation
- Key histologic DDX: Pneumocystis pneumonia (**get fungal stains**, esp. if immunocompromised)


Microliths of calcium phosphate within alveoli

ALVEOLAR MICROLITHIASIS

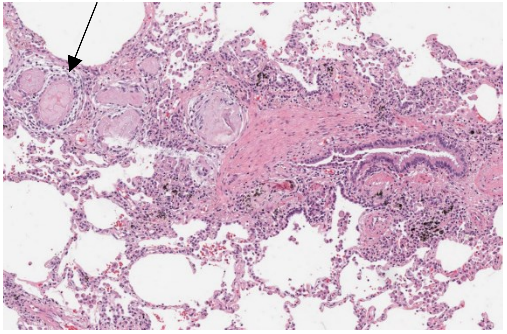
MORPHOLOGY

- Lamellated **microliths of calcium phosphate** within alveoli

OTHER HIGH YIELD POINTS

- AR mutations in **SLC34A2** with dysfunctional sodium phosphate transport
- Middle-aged adults, respiratory failure, indolent with slow progression
- **"Sandstorm"** appearance on radiology
- DDX: Corpora amylacea, dystrophic calcification, ossification

PULMONARY NODULES


Degenerating food particles

ASPIRATION

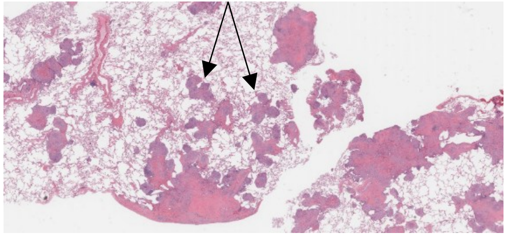
MORPHOLOGY

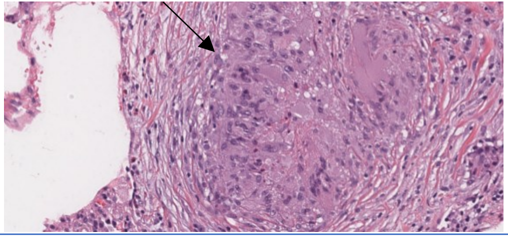
- **Airway-centered** inflammation with **giant cells** and organizing pneumonia
- Degenerating food particles may be **polarizable** (esp. some pill particles)
- Can also see lipoid pneumonia or abscess formation

OTHER HIGH YIELD POINTS

- Due to **aspiration of food particles**; can be single or multiple
- **Risk factors**: stroke, GERD, obesity, epilepsy, alcohol, dementia

Path presenter


Patchy lymphangitic distribution


Non-necrotizing granuloma

SARCOIDOSIS

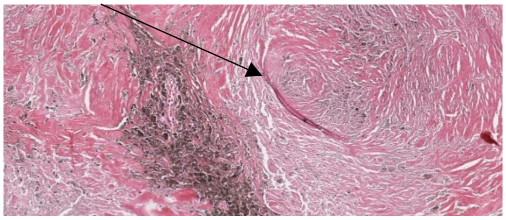
MORPHOLOGY

- Tightly formed, **non-necrotizing granulomas** with giant cells
- Granulomas eventually become confluent and mass-like
- Follows **lymphangitic distribution** (not in airspaces)
- No organizing pneumonia or interstitial inflammation
- Extensive fibrosis favors infectious etiology

OTHER HIGH YIELD POINTS

- **Systemic idiopathic granulomatous disease** with frequent pulmonary involvement, diagnosis requires clinical correlation
- **Starts centrally in lung** with large airways and hilar lymphadenopathy and extends outward with **progressive fibrosis**
- Giant cells can produce some endogenous polarizable material (calcium oxalate) – do not mistake as foreign material

Path presenter


Dense fibrous nodules

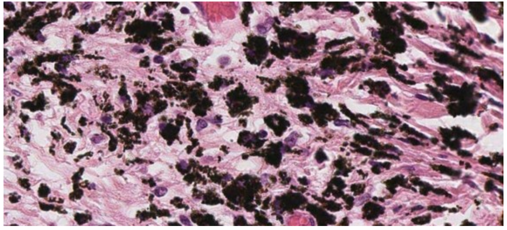
SILICOSIS

MORPHOLOGY

- Inhaled silica **engulfed by macrophages (birefringent** if polarized)
- **Form aggregates** that increasingly fibrose and hyalinize and eventually **coalesce into nodules**

OTHER HIGH YIELD POINTS

- Caused by **inhalation of silica** and related minerals
- Risk factors: Construction, manufacturing, mining


Numerous dust-laden macrophages

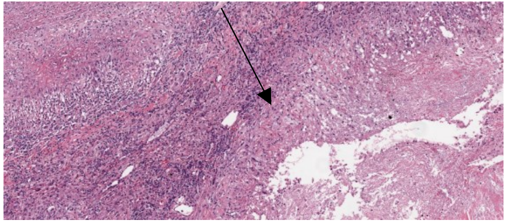
COAL WORKER PNEUMOCONIOSIS

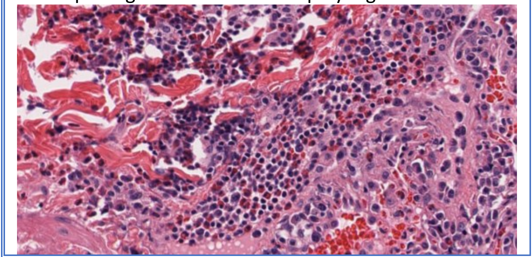
MORPHOLOGY

- Numerous **dust-laden macrophages** around bronchovascular bundles
- **Haphazard fibrosis** and emphysema; can progress to large nodules with fibrosis

OTHER HIGH YIELD POINTS

- Caused by **exposure** to coal dust – **"Black Lung Disease"**
- Common to see **concurrent silica/silicosis**


Necrotizing granulomatous inflammation


Eosinophilic granulomatosis with polyangiitis

VASCULITIS

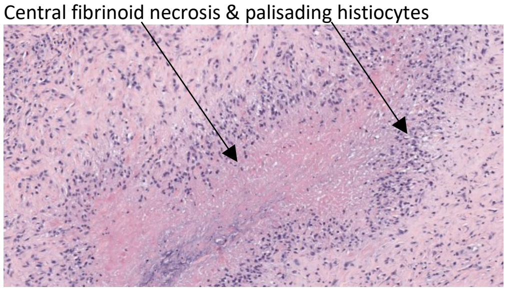
MORPHOLOGY

- **Granulomatosis with polyangiitis (Wegner's)**
    - **Necrotizing granulomatous inflammation**
    - Commonly impacts lung, nasal cavity, and kidney
    - In lung, see granulomas with geographic **central cavitating nodules**
    - In kidney can see crescentic glomerulonephritis
    - **PR3-ANCA positive**
- **Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)**
    - **Eosinophil-rich** and necrotizing granulomatous inflammation
    - Often impacts the lung; associated with asthma and eosinophilia
    - **MPO-ANCA positive**

OTHER HIGH YIELD POINTS

- Dx often involves **clinical/serologic correlation**

Path Presenter


Central fibrinoid necrosis & palisading histiocytes

RHEUMATOID NODULE

MORPHOLOGY

- **Granulomatous nodules** with **central fibrinoid necrosis**
- **Palisading histiocytes** with lymphoplasmacytic inflammation

OTHER HIGH YIELD POINTS

- **Most specific** pulmonary finding for rheumatoid arthritis is above histology
- DDX: Granulomatosis with polyangiitis, infection

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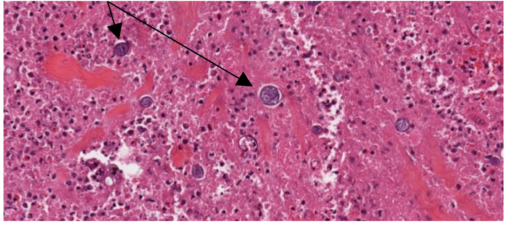
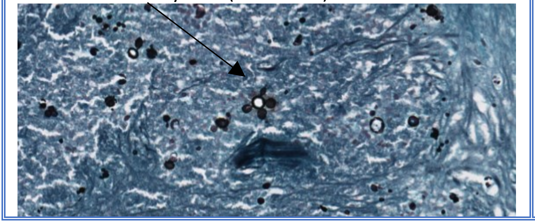

Coccidioidomycosis


Paracoccidioidomycosis (GMS stain)

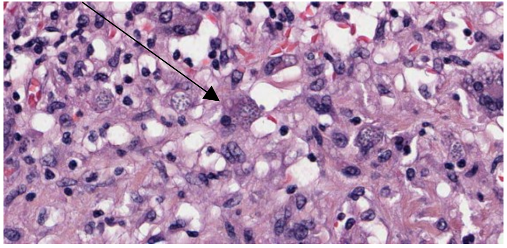
FUNGAL INFECTIONS

- Often diagnosed based on imaging and lab studies
- May be focal or diffuse (particularly if immunocompromised)
- Often cause **granulomatous response** (± necrosis)

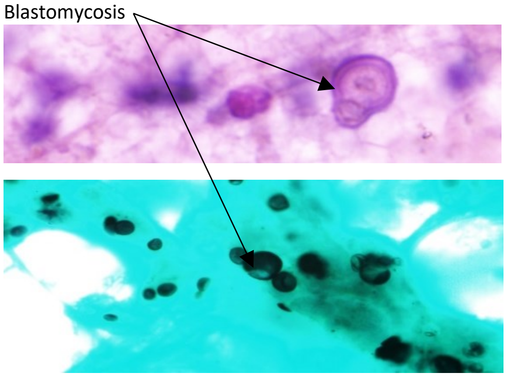
REGARDLESS OF IMMUNE STATUS

- **Coccidioidomycosis**
    - Southwestern United States in dry soil (Valley fever)
    - Spherules with endospores
- **Paracoccidioidomycosis**
    - South and Central America
    - Fungal forms with **radial pattern**
- **Histoplasmosis**
    - Mississippi/Ohio River valley in soil and caves (bat droppings)
    - **Small, narrow-based buds**
    - Common to have subclinical infection with burnt out hyalinized granulomas

Histoplasmosis



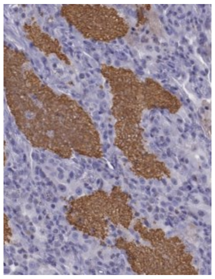
Blastomycosis



- **Blastomycosis**
    - Mississippi/Ohio River valley and Northeast in soil
    - **Broad-based buds** with round, uniform, thick double wall

IMMUNOCOMPROMISED

Pneumocystis jirovecii IHC



- **Pneumocystis pneumonia**
    - Ubiquitous; immunocompromised hosts
    - Crushed ping pong balls with a central dot in foamy alveolar exudate
- **Cryptococcosis**
    - Ubiquitous in soil and bird dropping
    - Round, **thick halo**; variable size; narrow budding
- **Aspergillosis**
    - Ubiquitous in soil
    - Septa hyphae with **45-degree** branching
    - Can colonize and form an aspergilloma ("fungus ball"); angioinvasive
- **Candidiasis**
    - Ubiquitous in skin (can be oral contaminant in BAL)
    - Budding yeast and pseudohyphae
- **Mucormycosis**
    - Ubiquitous; classically in poorly controlled diabetics
    - Broad ribbon-like hyphae with irregular branching

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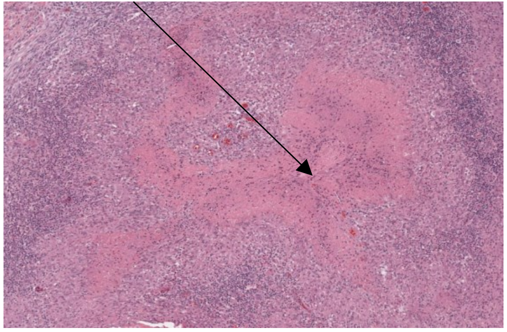
Caseating granuloma of TB



BACTERIAL INFECTIONS

Mycobacterium tuberculosis:

- Necrotizing/caseating granulomas and fibrosis (low threshold for AFB stain)
- Worldwide, many are asymptomatically infected leaving behind calcified nodules/nodes (Gohn complex), which can reactivate to cavitating infection

Nocardiosis:

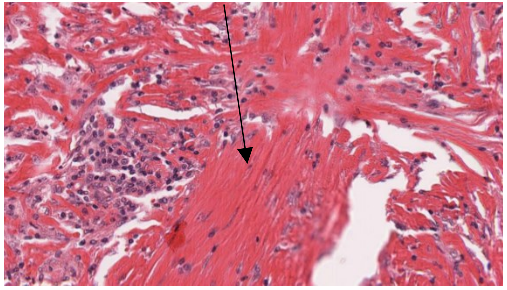
- Gram-positive filamentous bacteria in immunocompromised
- Highlighted by both AFB and GMS as slender tangled strings

Path Presenter

Actinomycosis

- Gram-positive filamentous bacteria (commensal in the oral cavity)
- Can cause abscesses with distinctive "**sulfur granules**"

Acellular hyalinized collagen



PULMONARY HYALINIZING GRANULOMA

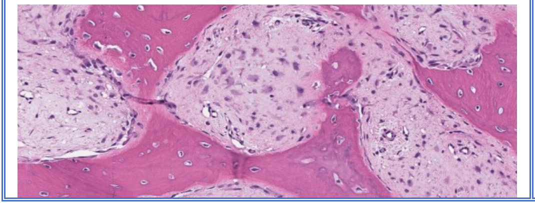
MORPHOLOGY

- Single or multiple **slow-growing** nodules
- **Well-circumscribed**, acellular hyalinized collagen
- Scattered foci of chronic inflammation

OTHER HIGH YIELD POINTS

- The pulmonary counterpart to fibrosing mediastinitis
- Often considered an **exaggerated response to a remote infection**, most often **histoplasmosis**
- Can also be associated with **IgG4-related disease**

Mature lamellar bone



METAPLASTIC OSSIFICATION

MORPHOLOGY

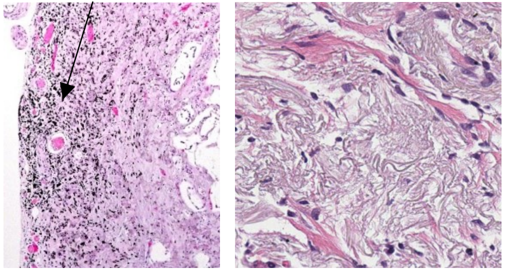
- Nodule(s) of **mature lamellar bone**

OTHER HIGH YIELD POINTS

- Often incidental finding
- Often formed in response to injury, such as scar, aspiration, granulomas, apical caps, etc.

3. PULMONARY PATHOLOGY

Subpleural scar, elastotic fibers with intermixed collagen



APICAL CAP

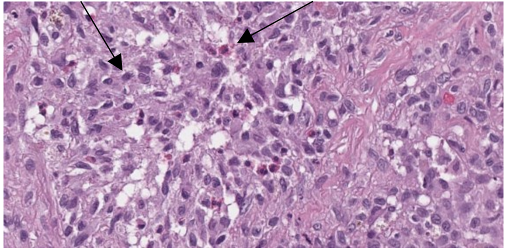
MORPHOLOGY

- **Subpleural** fibroelastotic scars
- Predominantly **elastotic fibers** with **intermixed collagen**
- Triangular-shaped with a broad pleural base

OTHER HIGH YIELD POINTS

- Seen most commonly in the apices of the upper lobes
- Unclear etiology; can radiographically mimic malignancy
- If diffuse, pleuroparenchymal fibroelastosis

Langerhans cells with admixed eosinophils



PULMONARY LANGERHANS CELL HISTIOCYTOSIS

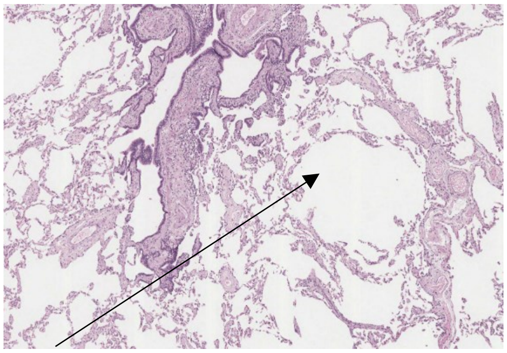
MORPHOLOGY

- **Eosinophils with numerous Langerhans** cells: amphophilic cytoplasm and nuclear grooves (“coffee beans”); **IHC (+) S100, langerin (CD207), CD1a**

OTHER HIGH YIELD POINTS

- Aka “eosinophilic granuloma”; strongly associated with **smoking**
- Considered a **reactive proliferation** (extrapulmonary LCH is neoplastic)
- Often presents as a cystic disease
- Electron microscopy shows Birbeck granules (tennis racket shaped)

MEDICAL LUNG DISEASE - NEAR NORMAL APPEARANCE



Airspace enlargement

EMPHYSEMA

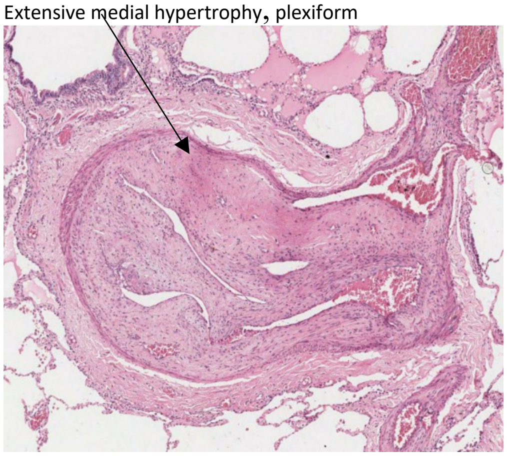
MORPHOLOGY

- **Airspace enlargement** due to alveolar septal destruction without significant fibrosis (common background/incidental finding)

OTHER HIGH YIELD POINTS

- Often classified by location:
  - **Centrilobular**: Destruction near small airways; associated with **smoking**, upper lobe predominant; emphysema + chronic bronchitis = COPD
  - **Panacinar**: Involves entire lobule from beginning; classically associated with **α1-antitrypsin deficiency**; lower-lobe predominant; risk of liver disease

Extensive medial hypertrophy, plexiform



PULMONARY HYPERTENSION

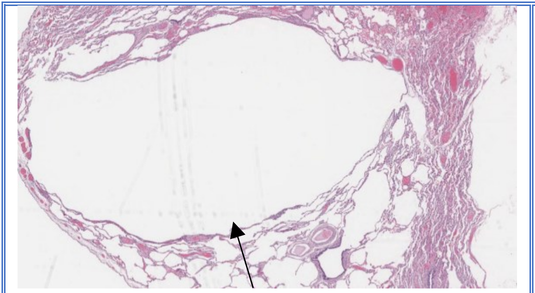
MORPHOLOGY

- **Medial hypertrophy** of arteries and veins
- **Intimal proliferation and fibrosis**
- Plexiform lesions, fibrous webs/plugs (colander-like), emboli/thrombi

OTHER HIGH YIELD POINTS

- Usually in young females, presenting as an exercise intolerance
- **Clinical diagnosis**. Pathologic findings may not correlate with symptoms
- Increased pulmonary vascular pressure
- Common causes: heart failure, lung disease (e.g., UIP)
- Can be primary or idiopathic
- Note: recanalized thrombi (from a PE) are also plexiform
- Inactivating mutation of BMPR2 gene

Path Presenter



Variably sized thin-walled cysts underneath pleura

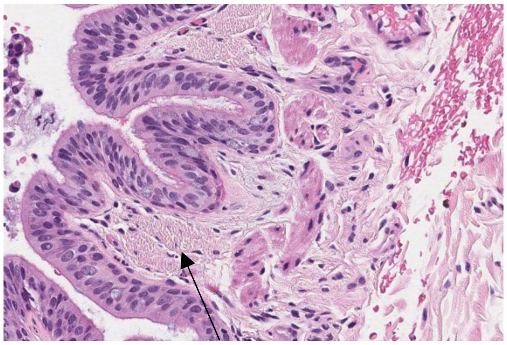
BIRT-HOGG-DUBE SYNDROME

MORPHOLOGY

- **Variably sized thin-walled cysts** underneath pleura near septa or lower lobes

OTHER HIGH YIELD POINTS

- **Multi-organ manifestations:**
  - Skin: Fibrofolliculomas
  - Kidney: Hybrid oncocytic neoplasms
  - Lung: Cysts → Can rupture to cause pneumothorax
- **Autosomal dominant,** mutations in **folliculin gene (FLCN)**



Scarring between epithelium and smooth muscle

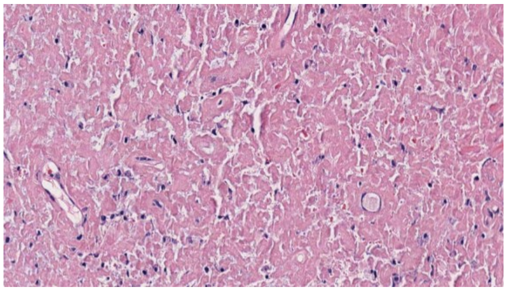
CONSTRICTIVE (OBLITERATIVE) BRONCHIOLITIS

MORPHOLOGY

- **Fibroinflammatory scarring** of bronchioles between epithelium and smooth muscle
- Can eventually **obliterate bronchiole lumen**
- **Elastin** stain highlights elastic layer of obliterated airway (usually with a remaining paired artery)

OTHER HIGH YIELD POINTS

- **Obliterative bronchiolitis** is a term primarily used in the transplant setting
- Possible causes: Infection, fumes/toxins, medications, connective tissue disease (especially rheumatoid arthritis)



Waxy pink protein deposition (amyloid)

AMYLOIDOSIS

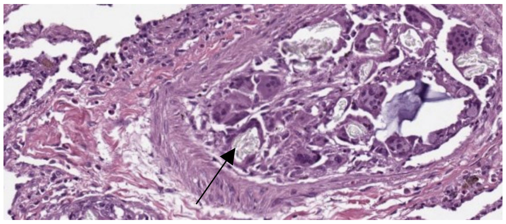
MORPHOLOGY

- **Waxy pink protein** deposition (**"apple green" birefringence** with Congo red**)**

OTHER HIGH YIELD POINTS

- Can be **localized or systemic**
- Localized pulmonary amyloidosis can be **nodular or diffuse**

Path Presenter



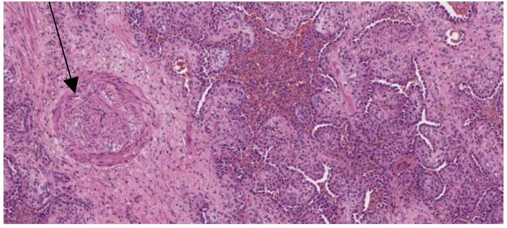
Foreign material embolism

FOREIGN MATERIAL EMBOLI

- **Intravenous drug use** associated with **microcrystalline cellulose emboli (**refractile under polarized light)
- Can also see bone marrow/fat emboli from bone fractures (especially after CPR)

Path Presenter

Intimal fibrosis of pulmonary venules



PULMONARY VENO-OCCLUSIVE DISEASE (PVOD)

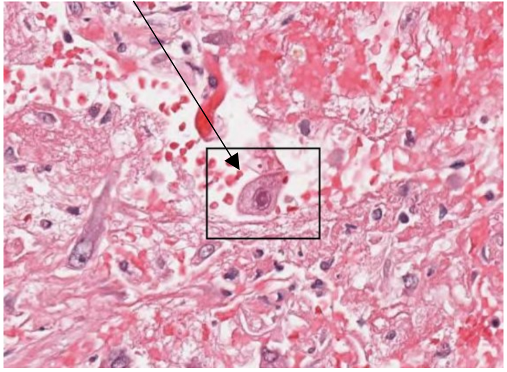
MORPHOLOGY

- Pulmonary venules with **intimal fibrosis** and diffuse smooth muscle narrowing
- **Post-capillary proliferation** with interstitial and alveolar hemosiderin-laden macrophages

OTHER HIGH YIELD POINTS

- Rare cause of pulmonary hypertension
- Diagnosis confirmed by lung biopsy

Cytomegalic cells with basophilic nuclear inclusion



CMV PNEUMONITIS

MORPHOLOGY

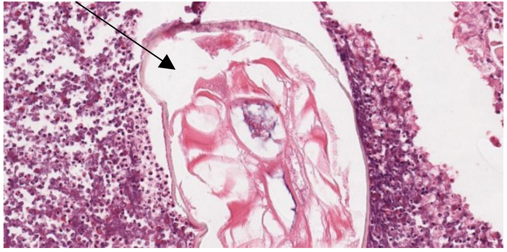
- Infected cells are **large with prominent basophilic nuclear inclusion** (highlight with PAS and GMS), often with a clear halo
- Smaller basophilic cytoplasmic inclusions are also present
- Chronic inflammation, edema, pneumocyte hyperplasia, hemorrhagic necrosis
- In the lung, CMV usually infects **endothelial cells and alveolar histocytes**

OTHER HIGH YIELD POINTS

- IHC staining for CMV is confirmatory

Path Presenter

Dirofilaria organism



DIROFILARIA (CANINE HEARTWORM)

MORPHOLOGY

- Roundworm infection with longitudinal ridges on the cuticle

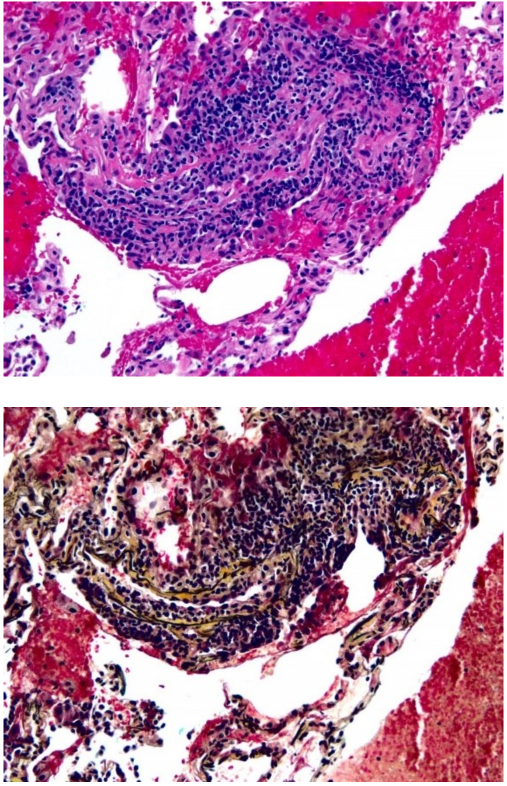
OTHER HIGH YIELD POINTS

- Blood-born parasite, can see worm moving across the **cornea in the eye**
- Serious and possibly fatal infection

Path Presenter

MEDICAL LUNG DISEASE – TRANSPLANT

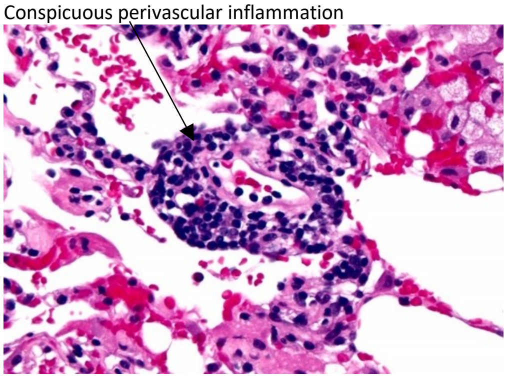
Perivascular and interstitial lymphocytes



ACUTE CELLULAR REJECTION

Grading: Acute Transplant Rejection	
Alveolar Rejection	
Ax **(Ungradable)**	Inadequate sampling
A0 **(None)**	Normal pulmonary parenchyma without evidence of mononuclear cell infiltration, hemorrhage, or necrosis
A1 **(Minimal)**	Scattered, infrequent perivascular mononuclear infiltrates (particularly around venules), **< 3 cells thick**
A2 **(Mild)**	Conspicuous perivascular inflammation, **> 3 cells thick**
A3 **(Moderate)**	Conspicuous perivascular inflammation, with extension into **alveolar septa**
A4 **(Severe)**	Conspicuous perivascular inflammation, with features of **acute lung injury**
Bronchiolar Rejection	
Bx **(Ungradable)**	Inadequate sampling
B0 **(None)**	No significant airway inflammation
B1R **(Low-grade)**	**Submucosal** chronic inflammation, without significant intraepithelial inflammation or injury
B2R **(High-grade)**	Submucosal chronic inflammation with intraepithelial lymphocytes, epithelial injury, ± neutrophils, ulceration, and/or necrosis

Conspicuous perivascular inflammation



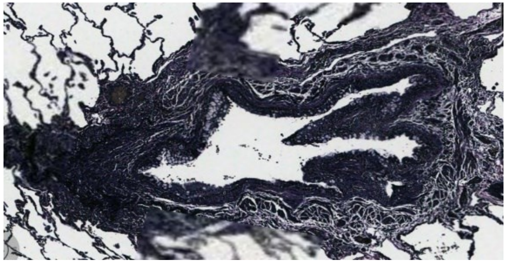
MORPHOLOGY

- Based on the presence of **perivascular and interstitial T cell-rich infiltrates**
- Can also see **lymphocytic bronchiolitis** with a band-like T cell-rich chronic inflammatory infiltrate in the submucosa of bronchioles (which have no cartilage in the walls) (vs. BALT, which is well-circumscribed and B cell rich)

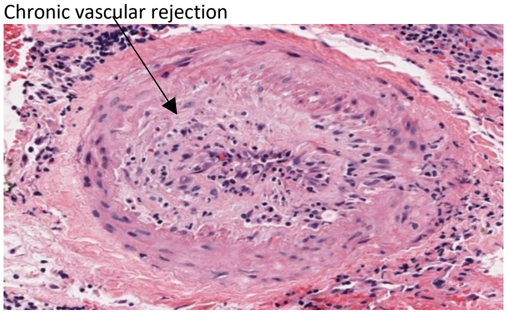
OTHER HIGH YIELD POINTS

- For adequate sensitivity, sampling should include **five fragments** of expanded, alveolated lung and multiple tissue levels
- Surveillance biopsies are often performed to look for rejection at regular post-transplant intervals (6, 9, 12 months)
- Perivascular/interstitial and bronchial chronic inflammation is **not specific** for rejection: Infection and PTLD can look similar, so consider other options, especially if there are many neutrophils or plasma cells

Obliterative bronchiolitis, elastic stain



Chronic vascular rejection



CHRONIC REJECTION

MORPHOLOGY

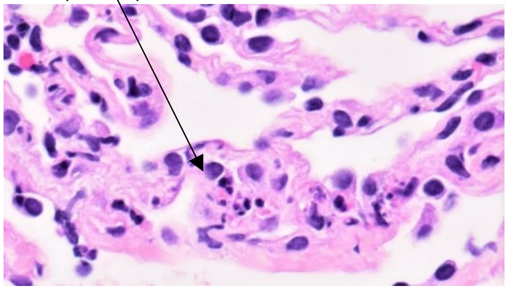
- **Obliterative bronchiolitis**: Progressive airway lumen obliteration by inflammation and fibrosis
- Elastic stain can be used to highlight obliterated bronchioles (synonymous with constrictive bronchiolitis in nontransplant setting)
- **Chronic vascular rejection**: Myointimal thickening and fibrosis within arteries and veins (not often seen in biopsies)

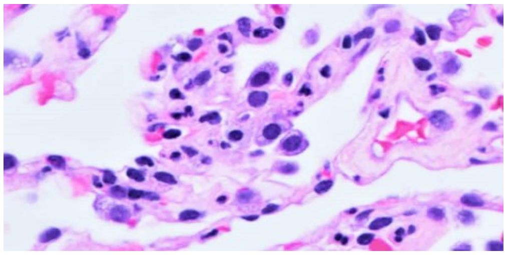
OTHER HIGH YIELD POINTS

- Hard to see on surveillance biopsies; often, a **clinical diagnosis** with reduced FEV1

GRADING: CHRONIC TRANSPLANT REJECTION	
OBLITERATIVE BRONCHIOLITIS	
C0	Absent
C1	Present
CHRONIC VASCULAR REJECTION	
D1	Absent
D0	Present

Neutrophilic capillaritis





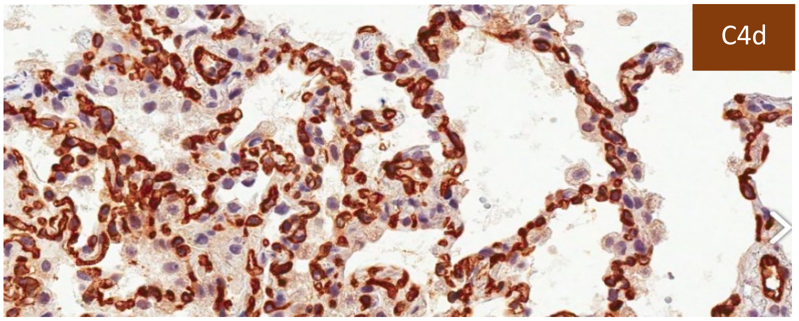
ANTIBODY-MEDIATED REJECTION

MORPHOLOGY

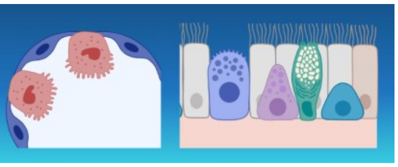
- **Neutrophilic capillaritis** and neutrophilic septal margination

OTHER HIGH YIELD POINTS

- Less well-defined than in other organs
- **Requires:** Clinical dysfunction, positive circulating donor-specific antibodies (DSA), and C4d immunoreactivity
- **IHC/IF: C4d** strong, linear/donut pattern in septal capillaries

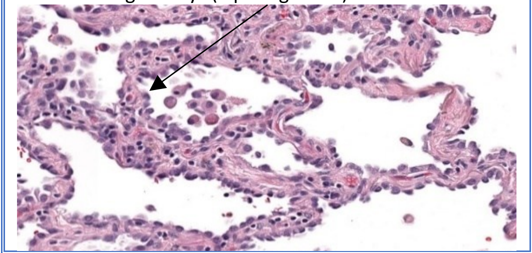


3. PULMONARY PATHOLOGY



EPITHELIAL PRECANCEROUS LESIONS AND CARCINOMAS

Growth along airways (lepidic growth)



ATYPICAL ADENOMATOUS HYPERPLASIA

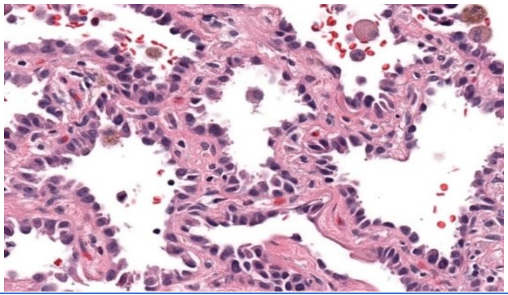
MORPHOLOGY

- **≤ 0.5 cm**, purely **lepidic** growth
- A **localized** proliferation of mildly to moderately atypical type II pneumocytes

OTHER HIGH YIELD POINTS

- Often **peripheral**
- Benign; cured with complete resection

Adenocarcinoma in situ



ADENOCARCINOMA IN SITU (FORMER BROCHOALVEOLAR CARCINOMA)

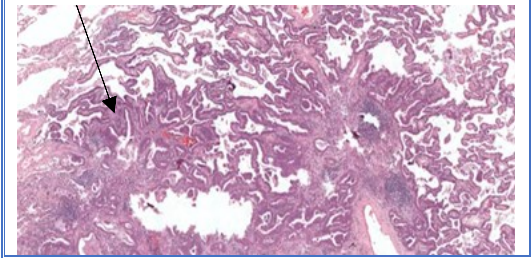
MORPHOLOGY

- **≤ 3 cm**, **solitary**, localized with pure **lepidic** growth
- No stromal, vascular, or pleural invasion; no spread through airspaces
- **Septal widening/sclerosis** is common, mild to moderate nuclear atypia

OTHER HIGH YIELD POINTS

- Mostly **non-mucinous**
- IHC: (+) CK7, TTF-1 and Napsin-A
- Benign; **100% survival** if completely resected
- Formerly “bronchoalveolar carcinoma” (BAC)

Small tumor with limited invasion



MINIMALLY INVASIVE ADENOCARCINOMA (MIA)

MORPHOLOGY

- Small tumor (**≤ 3 cm**)
- **Solitary**, predominantly **lepidic** growth, usually **non-mucinous**
- **Invasive component ≤ 0.5 cm** in greatest dimension

OTHER HIGH YIELD POINTS

- By definition, the absence of lymphovascular invasion, pleural invasion, spread through air spaces, tumor necrosis
- **100% survival** if completely resected

Diffuse distribution of mucinous adenocarcinoma

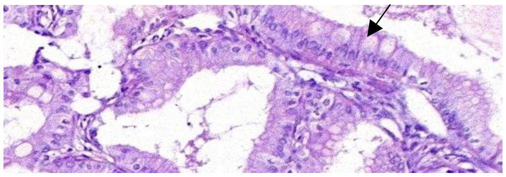


Image credits: Charles Leduc, MD

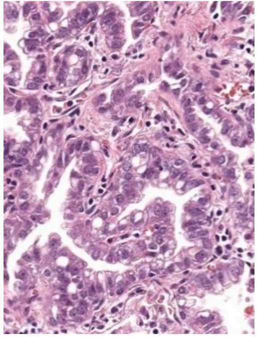
PNEUMONIC-TYPE ADENOCARCINOMA

MORPHOLOGY

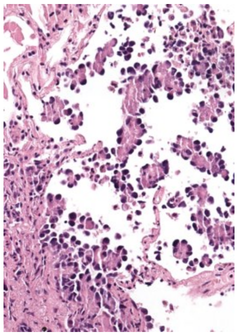
- Tumors should be considered “pneumonic adenocarcinoma” if there is **diffuse distribution** as opposed to a well-defined lesion of the lung
- Usually **mucinous** but can be non-mucinous
- Usually, **lepidic predominant,** but can be other patterns

ADENOCARCINOMA & VARIANTS

Papillary



Micropapillary

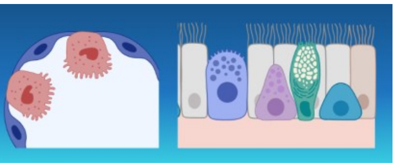


ADENOCARCINOMA

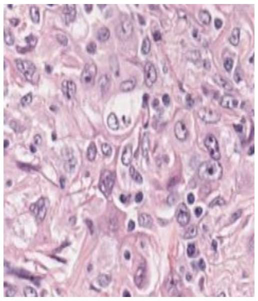
MORPHOLOGY

- Malignant epithelial tumor with glandular differentiation, mucin production, or pneumocyte marker expression
- **Criteria for invasion**: Histologic subtype other than lepidic, desmoplastic stroma associated with tumor, vascular or pleural invasion, spread through air spaces (STAS)

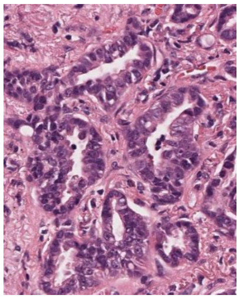
Histologic patterns	
Lepidic	Tumor growth along the surface of alveolar walls (non-invasive)
Acinar	Round to oval glands with a central lumen space surrounded by tumor cells



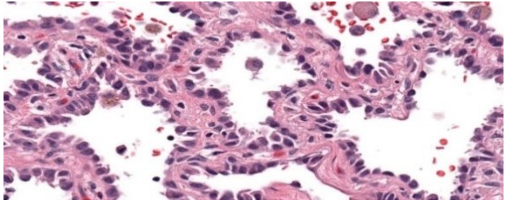
Solid



Acinar



Lepidic growth pattern



Papillary	Glands growing along central fibrovascular cores
Micropapillary	Cells growing in papillary tufts forming florets that lack fibrovascular cores (poorer prognosis)
Solid	Polygonal tumor cells growing in sheets (poorer prognosis)

OTHER HIGH YIELD POINTS

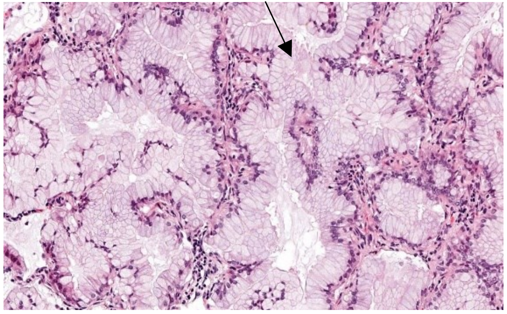
- Lung cancer is the **most common** cause of cancer-related death worldwide
- Strong association with tobacco **smoking**
- Other risk factors: Radon, air pollution, occupational exposure
- Symptoms vary, and most patients present late with advanced or metastatic disease
- CT often shows **peripherally located mass** with solid (invasive) areas of ground-glass (lepidic) areas
- **IHC: (+) TTF-1, Napsin-A, CK7**

Link Link Link Link

TTF-1/Napsin	p63	p40	CK5/6	Resection Dx	Biopsy Dx
+	-	-	-	Adenocarcinoma	NSCLC favor adenocarcinoma
+	+	-	-	Adenocarcinoma	NSCLC favor adenocarcinoma
+	+	+ (focal)	-	Adenocarcinoma	NSCLC favor adenocarcinoma
+	-	-	+ (focal)	Adenocarcinoma	NSCLC favor adenocarcinoma
-	Any one of the above diffusely positive			Squamous cell carcinoma	NSCLC favor SCC
-	Any one of the above focally positive			Large cell carcinoma	NSCLC, NOS
-	-	-	-	Large cell carcinoma	NSCLC, NOS

Note: Some primary lung adenocarcinomas, including mucinous adenocarcinoma, colloid carcinoma, and enteric adenocarcinoma, can be TTF-1 negative. They can even stain with CK20 and CDX2. These cases require clinical correlation to exclude a metastasis from the GI tract.

Abundant intracytoplasmic mucin



INVASIVE MUCINOUS ADENOCARCINOMA

MORPHOLOGY

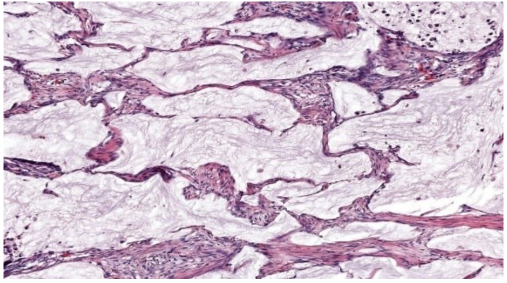
- Adenocarcinoma with **abundant intracytoplasmic mucin**

OTHER HIGH YIELD POINTS

- Any growth pattern may be seen
- **KRAS mutation**
- IHC: (+) CK7, CK20; (-) TTF-1
- Must exclude mucinous metastasis from a non-pulmonary primary

Path Presenter

Abundant mucin replacing air spaces



COLLOID ADENOCARCINOMA

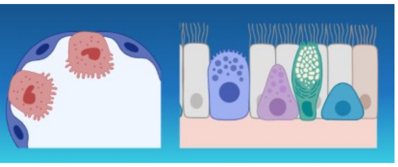
MORPHOLOGY

- Adenocarcinoma, where **pools of mucin** replace air spaces
- Mucin **distends alveolar spaces** and destroys walls
- Tumor cells often do not entirely line alveoli

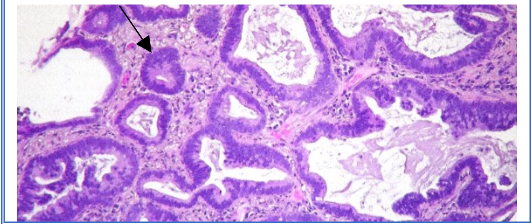
OTHER HIGH YIELD POINTS

- IHC: (+) CDX2, CK20; (+/-) TTF-1, CK7, Napsin-A

Path Presenter



Tall columnar cells



ENTERIC ADENOCARCINOMA

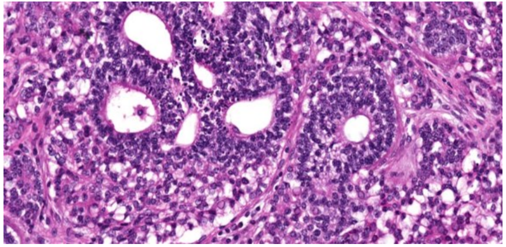
MORPHOLOGY

- Adenocarcinoma **resembling colorectal-type** adenocarcinoma
- Tall columnar cells with **pseudostratified** nuclei and abundant **"dirty" necrosis**

OTHER HIGH YIELD POINTS

- Requires careful clinical evaluation to **exclude metastasis**
- Morphology and IHC identical to colorectal carcinoma

Complex glandular structures



FETAL ADENOCARCINOMA

MORPHOLOGY

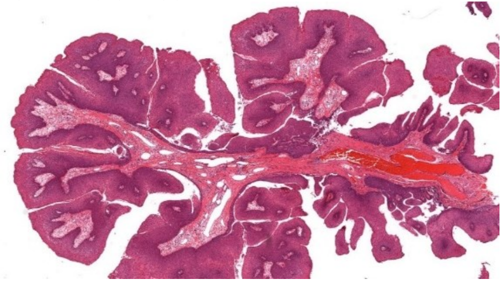
- **Complex glandular structures** composed of glycogen-rich, non-ciliated cells (resembling the developing epithelium of the fetal lung)
- Frequent **morule** formation
- Variable atypia

OTHER HIGH YIELD POINTS

- IHC: (+) TTF-1; frequent **nuclear b-catenin**, neuroendocrine and germ cell marker expression

SQUAMOUS LESIONS

Squamous papillary proliferation



SQUAMOUS PAPILLOMA

MORPHOLOGY

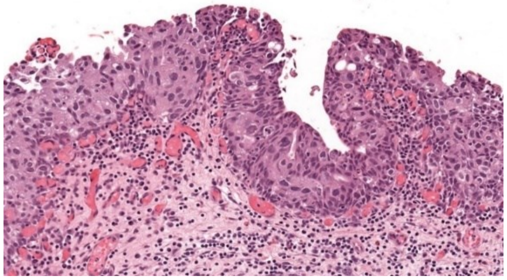
- **Papillary fronds** covered by squamous epithelium

OTHER HIGH YIELD POINTS

- **HPV(+)** in the majority of laryngotracheal papillomatosis
- Often presents with obstruction or hemoptysis
- Rare malignant transformation

Path Presenter

Non-invasive, dysplastic squamous epithelium



SQUAMOUS CELL CARCINOMA IN SITU

MORPHOLOGY

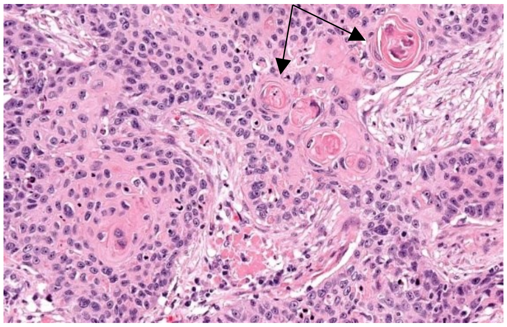
- Squamous dysplasia precursor lesion arising from the bronchial tree
- Part of a continuum with sequential molecular abnormalities

OTHER HIGH YIELD POINTS

- Respiratory epithelium → **irritant/carcinogen** → hyperplasia → squamous metaplasia → squamous dysplasia → SCC in situ → invasive SCC

PP Link PP Link

Well-differentiated SCC with keratinization



SQUAMOUS CELL CARCINOMA

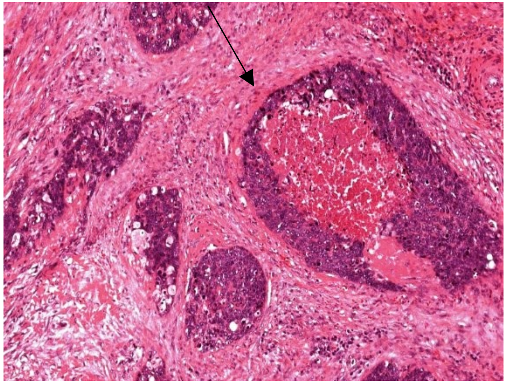
MORPHOLOGY

- **Keratinization**, **intercellular bridges**, or expression of squamous differentiation by IHC
- Can be non-keratinizing

OTHER HIGH YIELD POINTS

- Strongly associated with **smoking**, often **centrally located**
- **IHC: (+) p40, p63, CK5/6**; (-) TTF-1, Napsin-A

ADENOCARCINOMA	SQUAMOUS CELL CARCINOMA
TTF-1	p40 (most specific)
Napsin A	CK5/6
CK7 (less specific)	p63 (less specific)



Peripheral palisading, lobular architecture

BASALOID SQUAMOUS CELL CARCINOMA

MORPHOLOGY

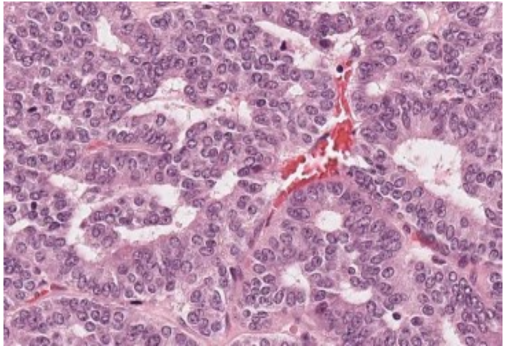
- Small cells with a **high N:C ratio**, distinct borders
- **Lobular** architecture with **peripheral palisading**; hyaline or mucoid stroma
- Lacks overt squamous histomorphology, numerous **mitoses**

OTHER HIGH YIELD POINTS

- Must comprise **> 50% of tumor**
- **IHC: (+/-) p40, p63, CK5/6**; (-) TTF-1, Napsin-A; Ki67 often 50-80%
- **Worse prognosis** than conventional SCC

Path Presenter

NEUROENDOCRINE TUMORS



Polygonal cells with “salt and pepper” chromatin

TYPICAL CARCINOID

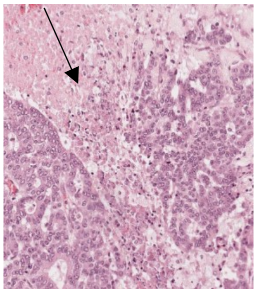
MORPHOLOGY

- Organoid or trabecular growth, **uniform polygonal cells**, finely granular **“salt and pepper”** chromatin, inconspicuous nucleoli, and eosinophilic cytoplasm
- **< 2 mitoses per 2 mm^2**, lacking necrosis, > 0.5 cm tumor size (if <0.5 cm, designated as “**tumorlet**”)

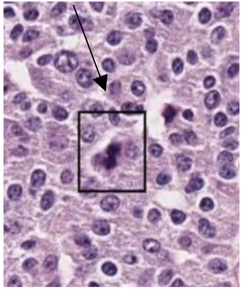
OTHER HIGH YIELD POINTS

- **Low-grade**; often arises near the **central airway** and can grow into the airway

Path Presenter



Necrosis



Mitotic activity

ATYPICAL CARCINOID

MORPHOLOGY

- A tumor with “carcinoid morphology”
- **2-10 mitoses per 2 mm^2** and/or **necrosis (often punctate)**

OTHER HIGH YIELD POINTS

- **Intermediate-grade** malignancy; worse prognosis than typical carcinoid

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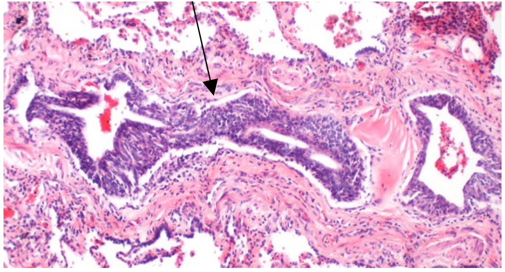


Proliferation of neuroendocrine cells along the airway

DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE CELL HYPERPLASIA

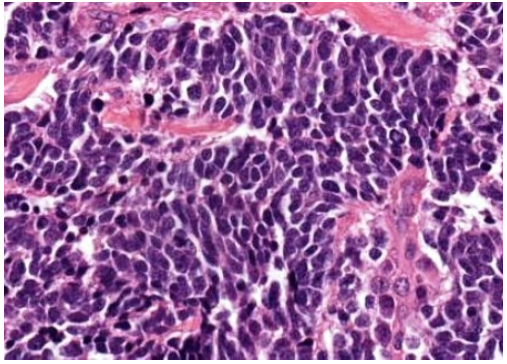
MORPHOLOGY

- Generalized proliferation of pulmonary **neuroendocrine cells along airways**

OTHER HIGH YIELD POINTS

- Often **older patients**
- May **invade locally**
- **Chronic progressive disease**
- Patients often present with cough and wheezing

Sheet-like growth of small cells with a high N:C ratio



SMALL CELL CARCINOMA

MORPHOLOGY

- **Small cells** (smaller than 3 resting lymphocytes), scant cytoplasm, molding
- **Densely cellular sheet-like growth**, finely granular chromatin (**no** nucleoli)
- High mitotic rate: **>10 mitoses per 2 mm^2**, frequent **necrosis**, Ki67 often approaching 100%

OTHER HIGH YIELD POINTS

- Often **centrally located** in major airways/hilar region
- Present with **rapid growth, metastases**
- Strongest association with heavy **smoking**, **very poor prognosis**

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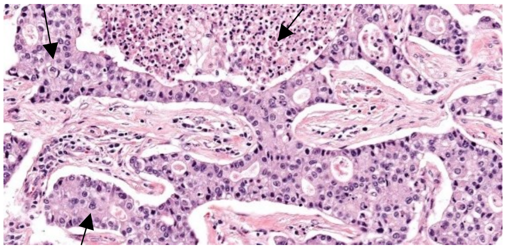
Trabecular architecture and necrosis



Large cells with neuroendocrine features

LARGE CELL NEUROENDOCRINE CARCINOMA

MORPHOLOGY

- **Neuroendocrine** morphology (architecture: organoid, nesting, palisading, rosettes, trabeculae)
- Cytologic features: **large cells** with abundant cytoplasm, vesicular chromatin, and **prominent nucleoli**
- **High mitotic rate, necrosis**

Path Presenter

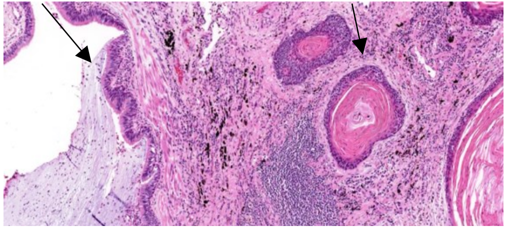
OTHER HIGH YIELD POINTS

- **Smoking**-related, often **peripheral**, **aggressive**

	Typical carcinoid	Atypical carcinoid	Large cell NE carcinoma	Small cell carcinoma
Smoking association	No	Maybe	Yes	Yes
Mitoses/2mm^2	0-1	2-10	>10 (median 70)	>10 (median 80)
Necrosis	No	Focal, if any	Yes	Yes, extensive
NE morphology	Yes	Yes	Yes	Yes
Ki-67	Up to 5%	Up to 20%	40-80%	Almost 100%
TTF-1 expression	Usually not	Usually not	~50%	~85%
Non-small cell component	No	No	Sometimes	Sometimes

- **IHC markers for neuroendocrine differentiation**: Synaptophysin, chromogranin, INSM1, CD56 (sensitive but less specific), NSE; Cytokeratin IHC often show perinuclear “dot-like” staining.
- Note: lung neuroendocrine neoplasms are **graded based on mitoses and necrosis** (counted in a hotspot). Ki67 may be helpful for confirmation but cannot be utilized for grading currently.

OTHER CARCINOMAS



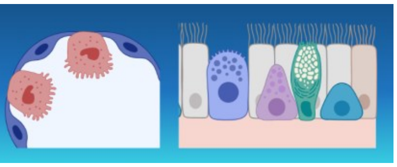
ADENOSQUAMOUS CARCINOMA

MORPHOLOGY

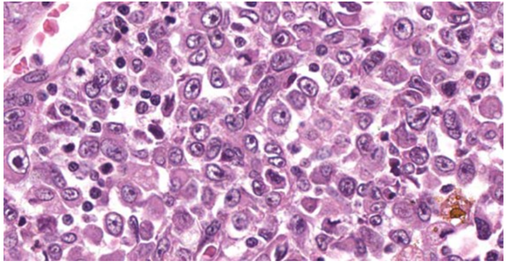
- Carcinoma with both **squamous component and adenocarcinoma component**
- Each must constitute **at least 10%**

OTHER HIGH YIELD POINTS

- Diagnosis can only on be made on resection specimens (not biopsy)



Large polygonal cells with prominent nucleoli



LARGE CELL CARCINOMA

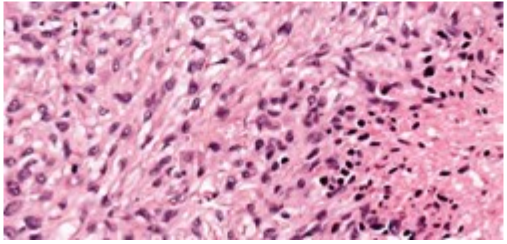
MORPHOLOGY

- **Undifferentiated, non-small cell carcinoma** that lacks cytologic, architectural, and IHC features of small cell carcinoma, adenocarcinoma, or SCC
- Sheets or nests of **large polygonal cells** with vesicular nuclei and **prominent nucleoli**

OTHER HIGH YIELD POINTS

- **Diagnosis of exclusion**, prevalence is decreasing
- IHC: **(+) cytokeratin**, (-) TTF-1, p40, synaptophysin, chromogranin

Sarcomatoid carcinoma with spindle cells



SARCOMATOID CARCINOMA

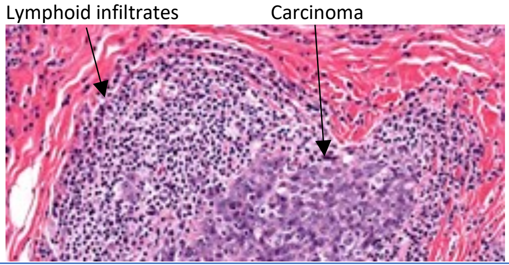
MORPHOLOGY

- **Spindle cell carcinoma**: Almost entire pure spindle cells
- **Giant cell carcinoma**: Numerous giant cells
- **Pleomorphic carcinoma**: Contains >10% giant cell or spindle cell carcinoma
- **Carcinosarcoma**: A mixture of NSCLC and sarcoma (poor prognosis)

OTHER HIGH YIELD POINTS

Path Presenter

- Diagnosis only on resection specimens; IHC variable



LYMPHOEPITHELIOMA-LIKE CARCINOMA

MORPHOLOGY

- Carcinoma with **marked lymphoid infiltrate**
- **Large cells** with syncytial growth, large vesicular nuclei, and prominent nucleoli

OTHER HIGH YIELD POINTS

Path Presenter

- **EBV infection** of neoplastic cells; **EBER ISH(+)**
- IHC: (+) cytokeratin AE1/AE3, CK5/6, p40, p63

MULTIPLE TUMORS

- When **more than one tumor nodule is identified** in resection samples, always attempt to distinguish synchronous primary tumors from a tumor with intrapulmonary metastasis:
- **Consider it a second primary (and stage each separately) if:**
  - ➢ Tumors have different histologic types (e.g., one squamous and one adenocarcinoma)
  - ➢ Tumors are dramatically different morphologically after a comprehensive review
  - ➢ Tumors are two squamous carcinomas, with each having an in situ component
- **Consider an intrapulmonary metastasis if:** Identical genetic abnormalities are detected
- **Relative arguments that favor a second primary:**
  - ➢ Different biomarker pattern
  - ➢ Absence of nodal or systemic metastases
- **Relative arguments that favor intrapulmonary metastasis:**
  - ➢ Matching appearance after a comprehensive review
  - ➢ Same biomarker pattern
  - ➢ Significant nodal or systemic metastases

PLEURAL INVASION

- If the tumor is approaching the visceral pleura, get an Elastin stain (EVG) to see if it crosses the elastic layer for staging purposes

Stage	Depth of invasion
PL0	Tumor does not completely traverse the elastic layer
PL1	Tumor extends through the elastic layer but not to the visceral pleural surface
PL2	Tumor extends to the visceral pleural surface
PL3	Tumor invades parietal pleura

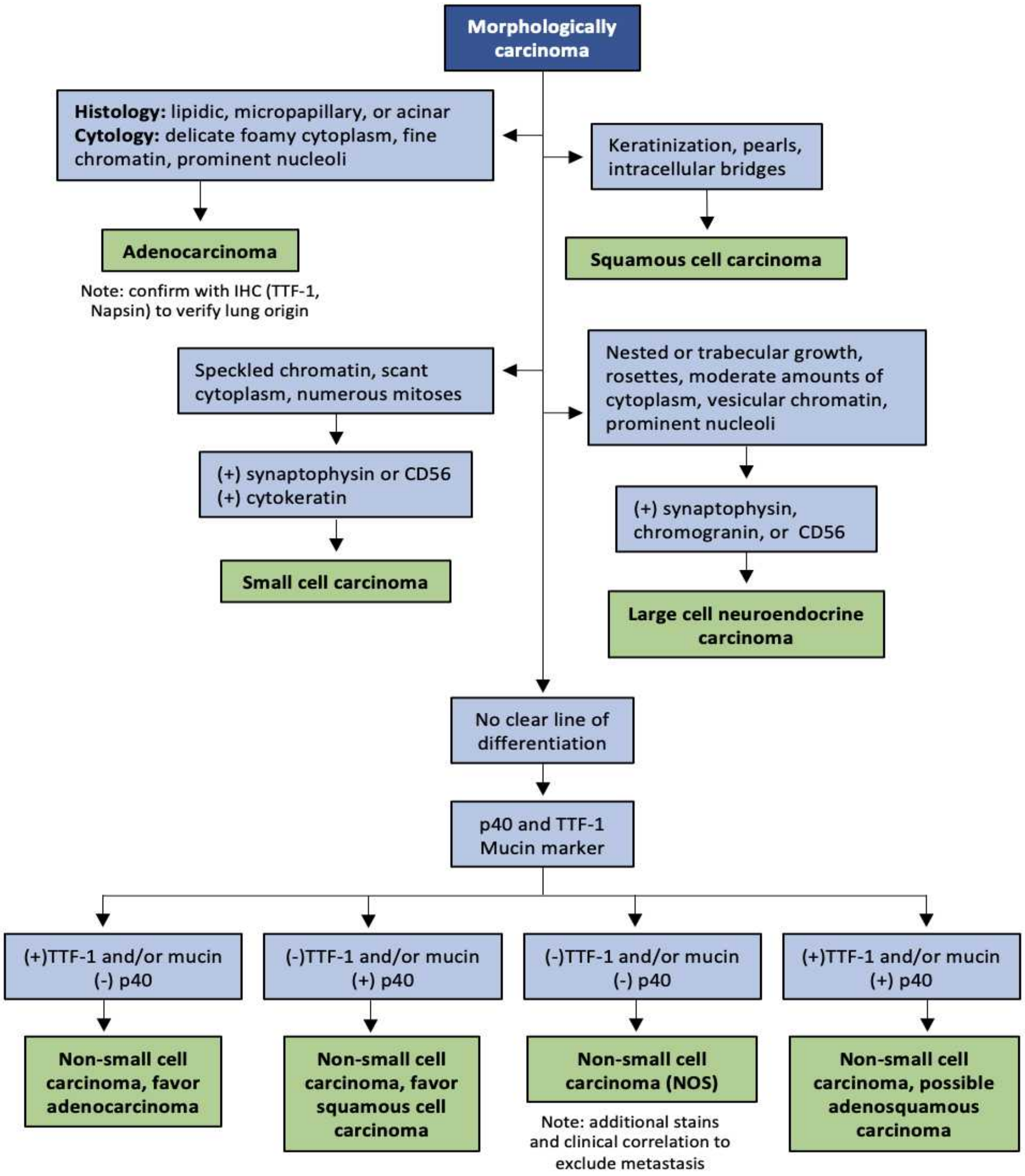
SPREAD THROUGH AIR SPACES (STAS)

- **Definition:** Micropapillary clusters, solid nests, or single cells of tumor extending beyond the edge of the tumor into the air spaces of the surrounding lung parenchyma
- No strict distance cut-off
- If present, **it cannot** be considered AIS or minimally invasive adenocarcinoma
- Associated with an **increased incidence of recurrence** in tumors that have undergone limited resection
- Should not be incorporated into measurement of tumor size

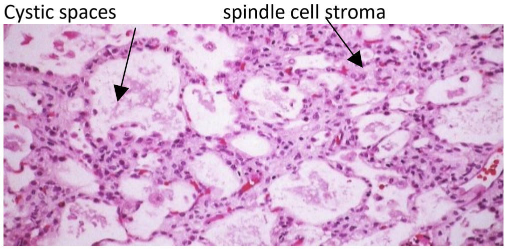
MOLECULAR PATHOGENESIS

- ~70% of lung cancers are inoperable; diagnosis and testing performed on biopsy or FNA
- Must test adenocarcinoma for: **EGFR, ALK, ROS1** in all cases (molecular/FISH/IHC); **PD-L1** (IHC)
- Considering testing for BRAF, KRAS, HER2, RET
- Can consider some of these tests in non-adenocarcinoma if mixed histology or small biopsy

CLASSIFICATION OF LUNG CARCINOMAS WITH LIMITED TISSUE


Morphologically carcinoma
Histology: lipidic, micropapillary, or acinar
Cytology: delicate foamy cytoplasm, fine chromatin, prominent nucleoli
Adenocarcinoma
Note: confirm with IHC (TTF-1, Napsin) to verify lung origin
Keratinization, pearls, intracellular bridges
Squamous cell carcinoma
Speckled chromatin, scant cytoplasm, numerous mitoses
(+) synaptophysin or CD56
(+) cytokeratin
Small cell carcinoma
Nested or trabecular growth, rosettes, moderate amounts of cytoplasm, vesicular chromatin, prominent nucleoli
(+) synaptophysin, chromogranin, or CD56
Large cell neuroendocrine carcinoma
No clear line of differentiation
p40 and TTF-1
Mucin marker
(+)TTF-1 and/or mucin (-) p40
Non-small cell carcinoma, favor adenocarcinoma
(-)TTF-1 and/or mucin (+) p40
Non-small cell carcinoma, favor squamous cell carcinoma
(-)TTF-1 and/or mucin (-) p40
Non-small cell carcinoma (NOS)
Note: additional stains and clinical correlation to exclude metastasis
(+)TTF-1 and/or mucin (+) p40
Non-small cell carcinoma, possible adenosquamous carcinoma

ADENOMAS


Cystic spaces
spindle cell stroma

ALVEOLAR ADENOMA

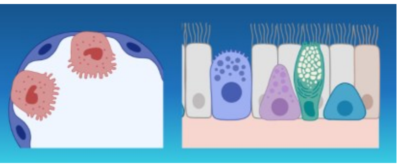
MORPHOLOGY

- Network of cystic spaces lined by a simple layer of type II pneumocytes overlying a spindle cell-rich stroma, sometimes with myxoid matrix

OTHER HIGH YIELD POINTS

- Solitary, well-defined, peripherally located
- Benign, very rare

3. PULMONARY PATHOLOGY



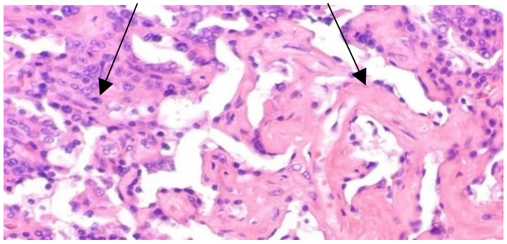


Image credits: Dr. Matthew Zaborowski, MD

SCLEROSING PNEUMOCYTOMA

MORPHOLOGY

- Pneumocytic origin with **dual cell populations**:
    - Small surface cuboidal cells: (+) cytokeratin, TTF-1, Napsin-A
    - Large stromal cells: (+) TTF-1, (-) cytokeratin
- Four growth patterns: solid, papillary, sclerotic, hemorrhagic

OTHER HIGH YIELD POINTS

- Benign, often asymptomatic, more commonly in women

OTHER ADENOMAS

MORPHOLOGY

- Glandular papilloma:
    - Benign, papillary, glandular tumor lined by ciliated or non-ciliated columnar cells with varying numbers of cuboidal and goblet cells
- Papillary adenoma:
    - Benign, circumscribed, papillary neoplasm that consists of cytologically bland, cuboidal to columnar cells covering fibrovascular cores
- Mucinous gland adenoma:
    - Benign, exophytic, well-circumscribed tumor of tracheobronchial seromucinous glands/ducts; microacini, glands, and tubules of bland cells

SALIVARY GLAND TUMORS

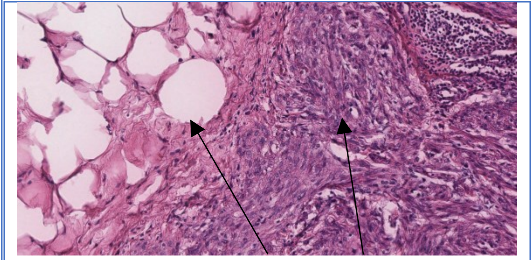
MORPHOLOGY

- **Mucoepidermoid carcinoma**: Triphasic tumor with mucin-secreting cells, squamous cells, and intermediate cells (MAML rearrangement)
- **Adenoid cystic carcinoma**: Basaloid carcinoma with epithelial and myoepithelial cells arranged in variable configurations (MYB rearrangement)
- **Epithelial-myoepithelial carcinoma**: Ducts of epithelial cells surrounded by myoepithelial cells, clear to spindled morphology
- **Pleomorphic adenoma**: Epithelial and myoepithelial cells intermingled with myxoid to chondroid stroma (PLAG1 rearrangement)

OTHER HIGH YIELD POINTS

- Arise from salivary-like glands in bronchi, often in the **central airway**

MESENCHYMAL TUMORS



Pulmonary hamartoma with fat and smooth muscle

PULMONARY HAMARTOMA

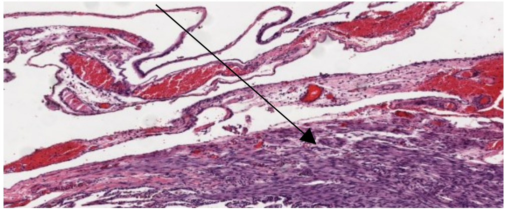
MORPHOLOGY

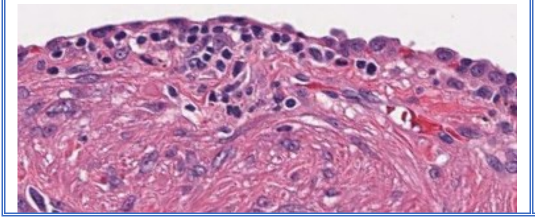
- **At least two mesenchymal elements** (e.g., **cartilage, fat**, smooth muscle, etc.) combined with **entrapped epithelium**

OTHER HIGH YIELD POINTS

- **Relatively common**
- Asymptomatic, benign, solitary, well-circumscribed
- Usually peripheral with **"popcorn" calcifications**
- Frequent **HMGA2 fusion**

Cysts with plump eosinophilic spindled cells





LYMPHANGIOLEIOMYOMATOSIS (LAM)

MORPHOLOGY

- Thin-walled cysts with **plump spindled cells** with pale eosinophilic/clear cytoplasm

OTHER HIGH YIELD POINTS

- Perivascular epithelioid cell tumor (**PEComa**)
- **Diffuse, bilateral, multicystic proliferation**, low-grade
- Exclusively young women and associated with **tuberous sclerosis**
- IHC: (+) **HMB45**, MelanA, MITF, SMA, desmin

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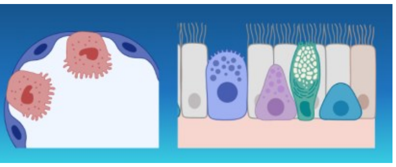
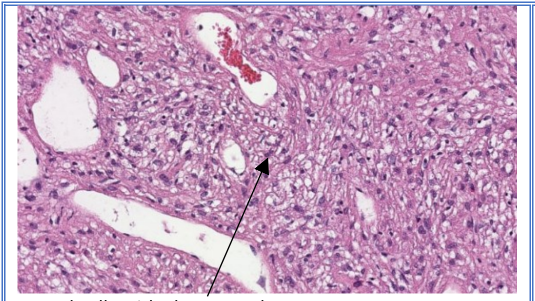
3. PULMONARY PATHOLOGY





Round cells with clear cytoplasm
Image credits: Farres Obeidin, MD, Northwestern University - Feinberg School of Medicine

CLEAR CELL ("SUGAR") TUMOR

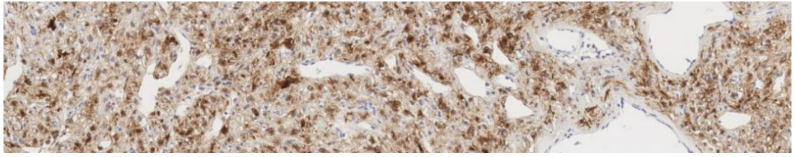
MORPHOLOGY

- Well-circumscribed lesion composed of round to oval cells with **abundant clear or eosinophilic cytoplasm** (PAS+ cytoplasmic glycogen)

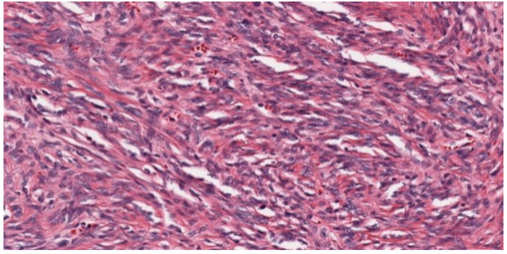
OTHER HIGH YIELD POINTS

- Rare, benign, solitary, peripherally localized **PEComa**
- IHC: (+) **HMB45**, MelanA, MiTF, MART-1, SMA, desmin

Image: MART-1



A patternless pattern of bland spindle cells



SOLITARY FIBROUS TUMOR (SFT)

MORPHOLOGY

- **A patternless pattern** of bland spindled cells with variable cellularity
- Collagenized stroma and **"staghorn" vessels** (dilated, thin-walled, branching)
- Can be hyalinized or myxoid

OTHER HIGH YIELD POINTS

- IHC: (+) **STAT6**, CD34, CD99
- Molecular: **NAB2-STAT6 gene fusion**
- Can also be seen as a tumor of the pleura

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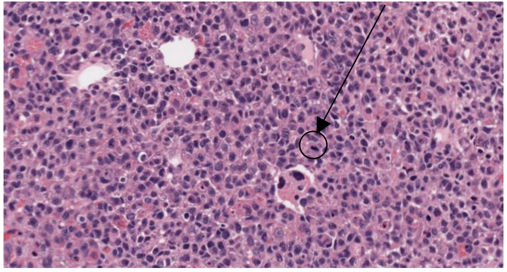
Variably pleomorphic cells with frequent mitoses



INTIMAL SARCOMA

MORPHOLOGY

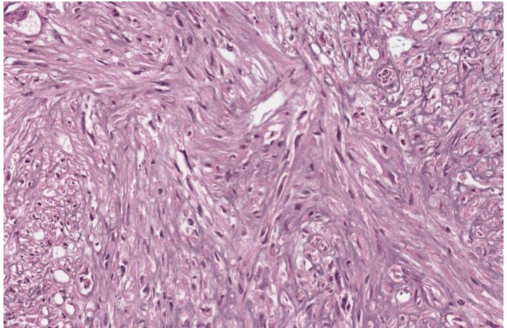
- Variably **pleomorphic spindled cells** with **necrosis and mitoses**

OTHER HIGH YIELD POINTS

- Malignant, arises in large blood vessels, characteristic **intraluminal growth** with obstruction of blood flow and tumor seeding
- IHC: (+) MDM2. Molecular: **Amplification of MDM2/CDK4**

Path Presenter

Bland spindle cells with fascicular / storiform pattern



INFLAMMATORY MYOFIBROBLASTIC TUMOR

MORPHOLOGY

- **Bland spindled to stellate cells** in myxoid to hyalinized stroma
- Can have **loose, fascicular, or storiform growth**
- Prominent lymphoplasmacytic infiltrate

OTHER HIGH YIELD POINTS

- Relatively **indolent**, usually solitary, frequently asymptomatic
- IHC: Variable staining with actin/desmin; **ALK(+)** with ALK gene rearrangements in ~50%

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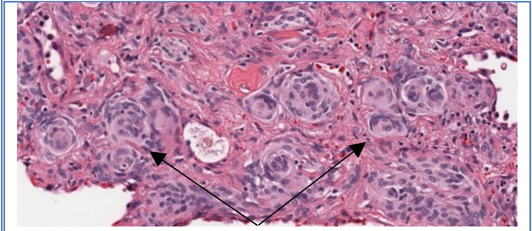


Bland oval cells forming whorls

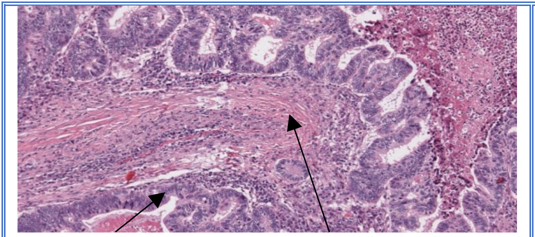
MENINGOTHELIAL-LIKE NODULE

MORPHOLOGY

- Monotonous, **bland, ovoid to spindle cells** within septa
- Indistinct cell borders, oval nuclei, **nuclear pseudoinclusions**
- **Whorled** architecture

OTHER HIGH YIELD POINTS

- Benign, common, incidental, often multiple, and small (1-4 mm)
- IHC: (+) **SSTR2A**, PR, EMA, CD56; (-) CK, S100, TTF1



PULMONARY BLASTOMA

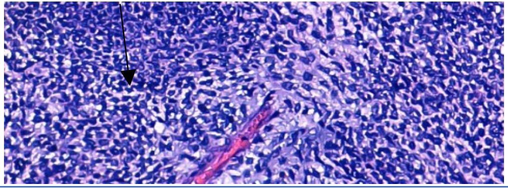
MORPHOLOGY

- **Biphasic tumor** with low-grade fetal adenocarcinoma and primitive mesenchymal stroma

OTHER HIGH YIELD POINTS

- Uncommon, usually in **adult patients**
- Poor prognosis

Small round primitive cells, sarcomatous differentiation



PLEUROPULMONARY BLASTOMA

MORPHOLOGY

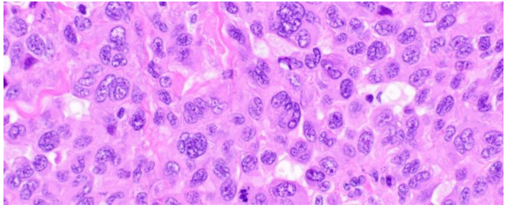
- **Small round primitive cells** with variable **sarcomatous** differentiation
- Can be solid or cystic

OTHER HIGH YIELD POINTS

- Sarcoma of the lung in **infancy/childhood**
- **DICER1 mutations**

(Image courtesy: Adriana Zucchiatti, MD**)**

Sheets of undifferentiated epithelioid cells



SMARCA4-DEFICIENT THORACIC SARCOMA

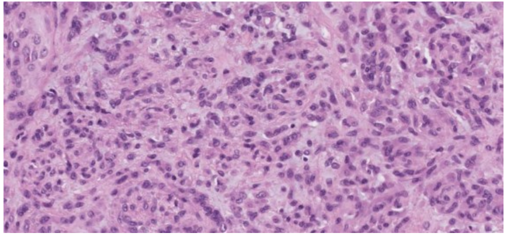
MORPHOLOGY

- **Diffuse sheets** of mildly discohesive, **undifferentiated epithelioid cells** with prominent nucleoli

OTHER HIGH YIELD POINTS

- Malignant, centered in the thorax, very **aggressive**
- IHC: (+) **CD34**, SALL4, (+/-) CK
- Molecular: **SMARCA4 mutations**

Strands and cords of round to spindle cells



PULMONARY MYXOID SARCOMA WITH EWSR1-CREB1 TRANSLOCATION

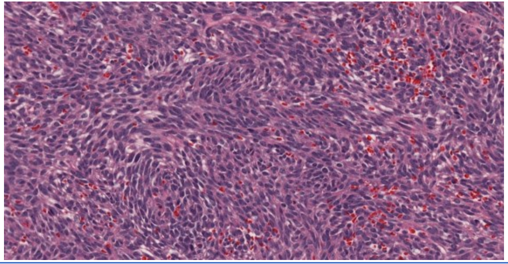
MORPHOLOGY

- Lobules of **delicate, lace-like strands and cords** of round to spindled cells within **myxoid stroma**

OTHER HIGH YIELD POINTS

- Malignant; usually arises in airways
- IHC: Generally negative except vimentin
- **EWSR1 rearrangements** with FISH

Uniform spindled cells with scant cytoplasm



SYNOVIAL SARCOMA

MORPHOLOGY

- Malignant **spindle cell neoplasm** with uniform nuclei, scant cytoplasm, and frequent **staghorn vessels**
- **Monophasic** (spindled only) or **biphasic** (spindled & epithelioid components)

OTHER HIGH YIELD POINTS

- t(X;18), **SS18-SSX gene fusions**
- IHC: (+) **CD99, TLE-1**; patchy EMA and CK
- **Poor prognosis**, usually young adults

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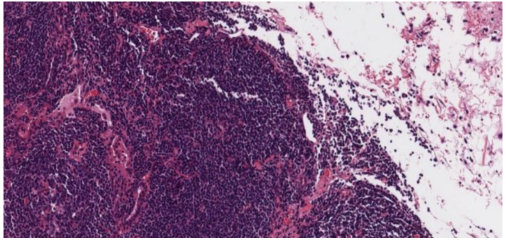
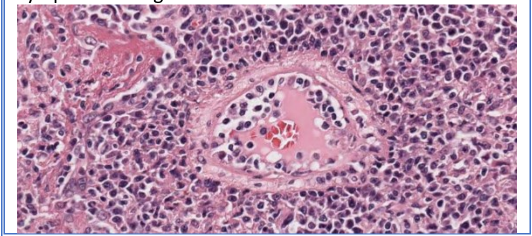
MISCELLANEOUS PULMONARY TUMORS

MALT lymphoma of the lung



- **Metastasis**
  - Always a consideration in the lung, especially if multiple or bilateral
- **MALT Lymphoma**
  - Thought to arise secondary to inflammatory conditions or autoimmune process

Lymphomatoid granulomatosis



- **Lymphomatoid Granulomatosis**
    - ➢ Pulmonary nodules composed of angiocentric and angiodestructive polymorphous lymphoid infiltrates, including reactive T cells and EBV(+) B cells
- **Germ Cell Tumors**
    - ➢ Mature teratoma most common

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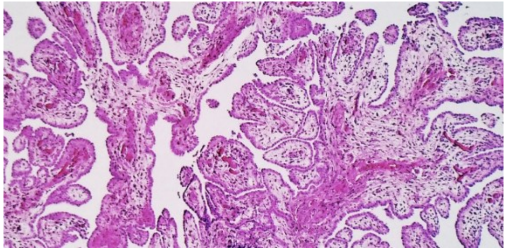
- **Intrapulmonary Thymoma**
- **Melanoma**

NON-NEOPLASTIC LESIONS OF THE PLEURA & PERITEONEUM

REACTIVE MESOTHELIAL HYPERPLASIA	MESOTHELIOMA
Absence of stromal invasion - beware of entrapment and tangential sectioning	Stromal invasion is usually apparent - highlight with pancytokeratin staining
Cellularity may be prominent	Dense cellularity
Simple papillae; single cell layers	Complex papillae; tubules, and cellular stratification
Loose sheets of cells without stroma	Cells surrounded by stroma
Necrosis rare	Necrosis occasionally present
Inflammation common	Minimal inflammation
Uniform growth	Expansile nodules, disorganized growth

Simple papillae with single cell layer



Courtesy: Laura G. Pastrián, MD

REACTIVE MESOTHELIAL HYPERPLASIA

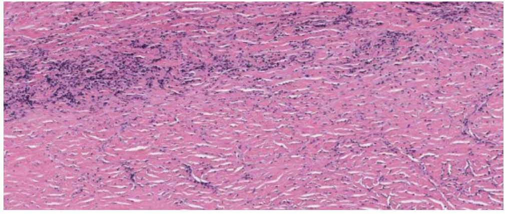
MORPHOLOGY

- **A reactive proliferation** of mesothelial cells with **several architectural patterns** (solid, nested, papillary, cord-like, etc.)
- Common **worrisome findings**: high cellularity, mitoses, cytologic atypia, papillary groups, and entrapment of mesothelial cells (mimicking invasion)

OTHER HIGH YIELD POINTS

- Reactive mesothelial cells responding to inflammation/irritation
- Can **histologically mimic mesothelioma/carcinoma**

Hypocellular fibrous tissue deposition



FIBROUS PLEURISY

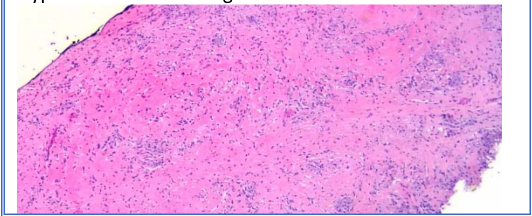
MORPHOLOGY

- Deposition of **bland, hypocellular fibrous tissue** in the pleura

OTHER HIGH YIELD POINTS

- Often involves the **visceral pleura** and may produce apical fibrous “capping”
- Severe cases can obliterate the pleural space
- May be associated with connective tissue disorders and chronic inflammation
- Can **mimic desmoplastic mesothelioma**

Hypocelluar dense collagen



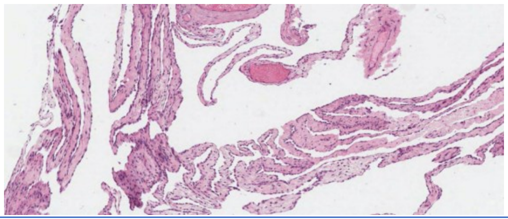
PLEURAL PLAQUE

MORPHOLOGY

- **Hypocellular, dense bundles of hyalinized collagen**, often with a “basket weave” arrangement
- Often dystrophic **calcifications**, variable chronic inflammation

OTHER HIGH YIELD POINTS

- Usually on **parietal pleura**, particularly on the diaphragm; **asbestos** exposure



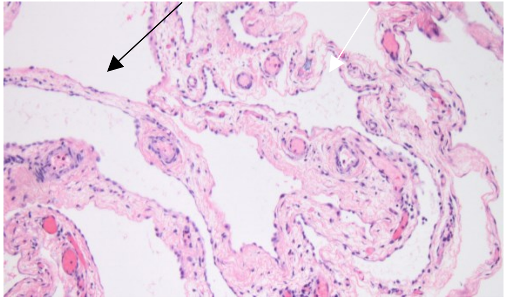
PERITONEAL INCLUSION CYST

MORPHOLOGY

- Single or multiple, **small, thin-walled, translucent, unilocular cysts**
- Attached or free in the peritoneal cavity
- Lined by a **single layer** of flattened, benign-appearing mesothelial cells

OTHER HIGH YIELD POINTS

- Often discovered **incidentally**, more common in **women**



A single layer of flattened hobnailed mesothelial cells

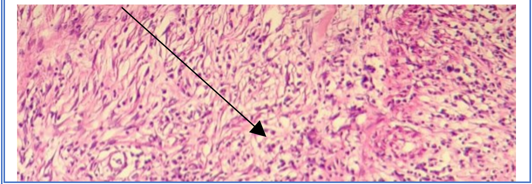
BENIGN MULTICYSTIC PERITONEAL MESOTHELIOMA

MORPHOLOGY

- Grossly: often **large, multiple, thin-walled, translucent, unilocular** cysts that may be attached or free floating
- Often fibrous tissue in septa with sparse inflammation
- Cysts are lined by a **single layer** of flattened to cuboidal mesothelial cells with a hobnailed appearance

OTHER HIGH YIELD POINTS

- Young to middle-aged **women** in the peritoneum/pelvis
- **Associations:** Previous abdominal surgery, pelvic inflammatory disease, and endometriosis; strong tendency to recur



Chronic inflammation and fibrosis

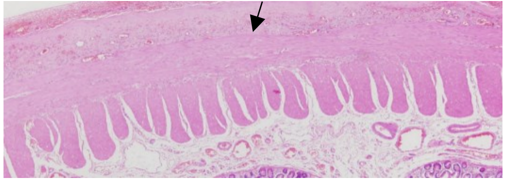
SCLEROSING MESENTERITIS

MORPHOLOGY

- Varying degrees of **fat necrosis, chronic inflammation, and fibrosis**, usually involving the **mesentery**

OTHER HIGH YIELD POINTS

- Rare, idiopathic, forms a **distinct mass** involving the small bowel mesentery



Bowel encapsulated by fibrous tissue

Courtesy: Dr. I Ruz-Caracuel

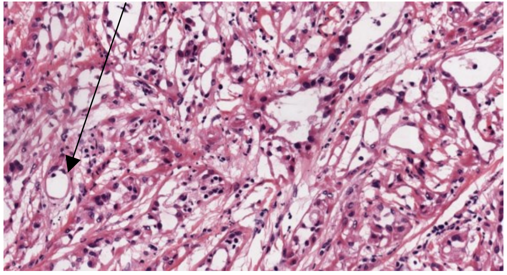
SCLEROSING PERITONITIS

MORPHOLOGY

- **Encasement of the bowel** by fibrous tissue

OTHER HIGH YIELD POINTS

- Rare, causes **bowel obstruction**
- Can be idiopathic or seen with intraperitoneal dialysis, VP shunts, and fibrothecomas of the ovary



Gland-like microcystic spaces with flattened cells

ADENOMATOID TUMOR

MORPHOLOGY

- **Irregularly shaped gland-like microcystic spaces** composed of flattened or cuboidal cells with associated fibrous stroma
- Bland cytologic features and **thread-like bridging strands**

OTHER HIGH YIELD POINTS

- Solitary, localized, most commonly in the **female genital/genitourinary tract** but can also be pleural

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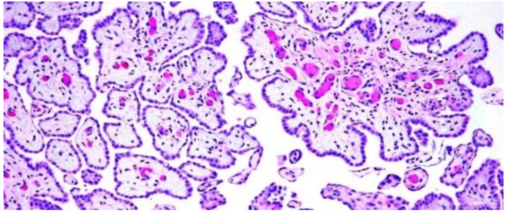


Papillary architecture with a single layer of cells

WELL-DIFFERENTIATED PAPILLARY MESOTHELIOMA

MORPHOLOGY

- Gross: **Velvety** appearance
- Prominent **papillary architecture with myxoid cores** covered by a single layer of flattened to cuboidal bland epithelioid cells

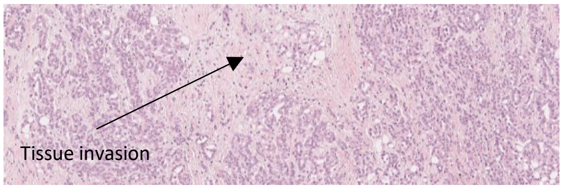
OTHER HIGH YIELD POINTS

- Rare, indolent, most cases cured by excision but may recur

Image credits: Gladell Paner, MD

MALIGNANT MESOTHELIAL TUMORS

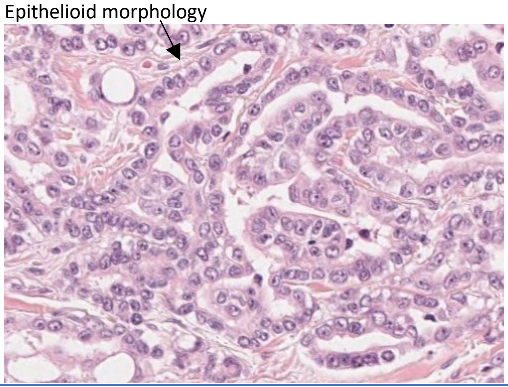
- **Demonstration of tissue invasion** is often key for the diagnosis but is not required when a substantial amount of solid tumor is present
- Common histologic patterns: **solid, tubulopapillary, trabecular**
- Special studies: **Use IHC to confirm mesothelial** and not a metastatic carcinoma (**always use a panel**)
- **IHC: BAP1 or MTAP loss, FISH: CDKN2A deletion**; multigene expression profiling panels.
- These studies support the diagnosis of mesothelioma with good (but not great) specificity
- Look for cytokeratin-positive malignant cells in regions in which they would not normally be present: adipose tissue, skeletal muscle deep to the parietal pleura, or lung tissue
- Benign processes tend to be well-circumscribed. Malignant processes tend to be poorly circumscribed and invasive



IMMUNOHISTOCHEMISTRY PANEL

Metastatic adenocarcinoma	Squamous cell carcinoma	Mesothelial cells
BerEP4	p40	Calretinin
B72.3	p63	D2-40
MOC31	MOC31	WT-1
Claudin-4	Claudin-4	CK5/6

Epithelioid morphology



EPITHELIOID MESOTHELIOMA

MORPHOLOGY

- **Malignant** proliferation of mesothelial cells with **epithelioid morphology**
- Often bland cytologically with eosinophilic cytoplasm and vesicular chromatin

OTHER HIGH YIELD POINTS

- Usually **diffuse** (circumferential, rind-like) with a **poor prognosis**
- Rarely, localized with a better prognosis
- Most common in **elderly males**; **asbestos exposure**; insidious onset

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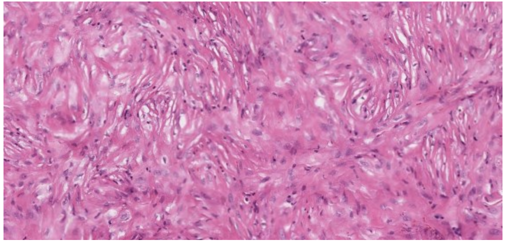
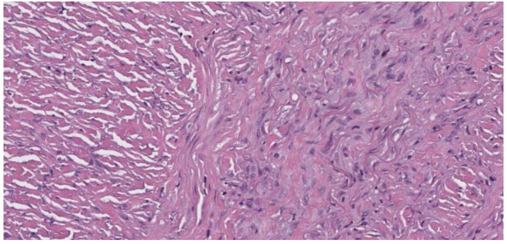
Haphazard spindle cells (sarcomatoid mesothelioma)



Infiltrating malignant cells in desmoplastic stroma



MESOTHELIOMA VARIANTS

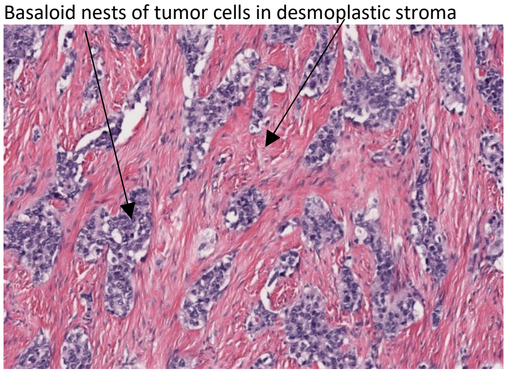
MORPHOLOGY

- **Sarcomatoid mesothelioma**
  - **Spindle cells arranged in fascicles** or haphazardly
  - Can see **heterologous elements** (e.g., rhabdomyosarcoma)
- **Desmoplastic mesothelioma**
  - **Dense collagenized tissue** with malignant mesothelial cells
  - Must be **>50% of the tumor**
  - Patternless or storiform pattern
  - **Invasion into fat** is most helpful to differentiate from organizing pleuritis
- **Biphasic mesothelioma**
  - Contains **both epithelioid and sarcomatoid patterns**, each >10%

OTHER HIGH YIELD POINTS

- Stroma invasion is often difficult to recognize
- **IHC: (+) pancytokeratin** (at least focally), helpful to demonstrate invasion
- **Loss of BAP1 is very uncommon in these types**
- **Worse prognosis** than epithelioid mesothelioma (desmoplastic <6 months)

Basaloid nests of tumor cells in desmoplastic stroma



DESMOPLASTIC SMALL ROUND CELL TUMOR

MORPHOLOGY

- **Basaloid nests** of small, uniform cells surrounded by **desmoplastic stroma**
- Hyperchromatic chromatin, scant cytoplasm, **frequent mitoses** & apoptosis

OTHER HIGH YIELD POINTS

- Malignant tumor of uncertain histogenesis; often in the peritoneal cavity of young men; poor prognosis
- IHC: (+) **Cytokeratins, desmin** (perinuclear dot-like pattern), EMA
- Molecular: **EWSR1-WT1 translocation**

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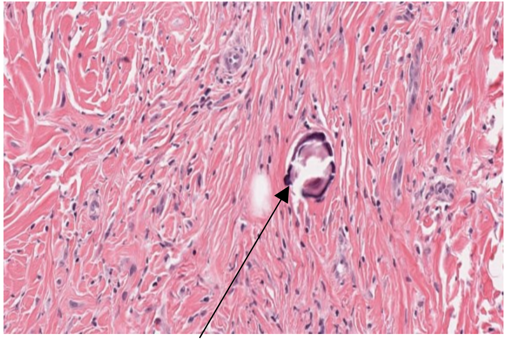
Hypocellular collagenized tissue

Psammomatous calcification

CALCIFYING FIBROUS TUMOR

MORPHOLOGY

- Paucicellular collagenized fibrous tissue with associated psammomatous or dystrophic calcifications
- **Circumscribed** but not encapsulated

OTHER HIGH YIELD POINTS

- Rare, **benign**, occurs in visceral pleura/peritoneum and **does not invade** underlying tissue
- More common in **younger women**
- IHC: (+) CD34; (-) STAT6, ALK, β-catenin

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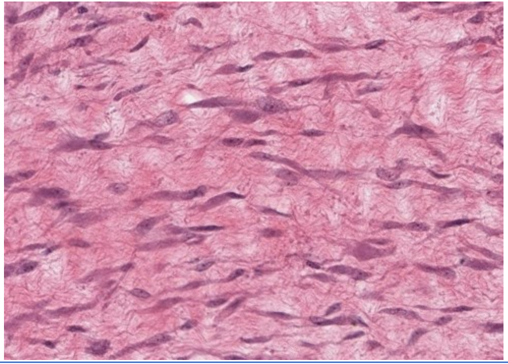
Infiltrating uniform, small spindle cells

DESMOID-TYPE FIBROMATOSIS

MORPHOLOGY

- **Infiltrative growth** into surrounding structures (skeletal muscle)
- **Broad, sweeping fascicles** of uniform spindled cells with pinpoint nucleoli
- Moderate amounts of **collagen** surrounding cells, slightly myxoid background

OTHER HIGH YIELD POINTS

- Benign, but **infiltrative** with a **high recurrence rate** (>50%)
- IHC: **(+) nuclear b-catenin**; (+/-) actin
- **Molecular:** mutations of FAP and APC/b-catenin (CTNNB1) pathway

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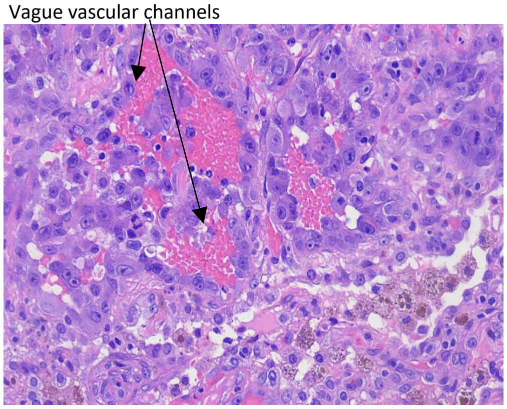
Vague vascular channels

ANGIOSARCOMA

MORPHOLOGY

- **Variable degrees of vascular differentiation**
- Some areas show well-formed anastomosing vessels, while other areas show solid sheets of high-grade cells
- Can be **epithelioid or spindled** cells, often with extensive **hemorrhage**
- Significant cytologic atypia, necrosis, and mitotic figures

OTHER HIGH YIELD POINTS

- Malignant, very **aggressive**, usually **elderly** patients
- IHC: (+) CD31, ERG, FLI1, often CD34

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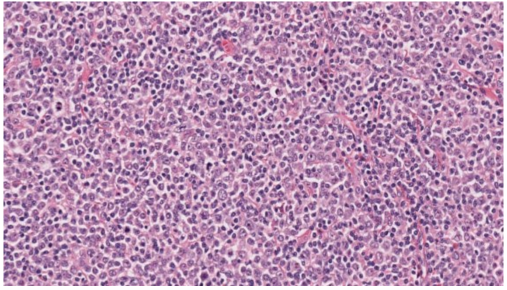
Diffuse large B-cell lymphoma

LYMPHOPROLIFERATIVE DISORDERS

- **Diffuse large B cell lymphoma associated with chronic inflammation**
    - **Resembles other forms of DLBCL** with large vesicular nuclei & prominent nucleoli
    - Occurs in patients with **long-standing pyothorax** or other chronic inflammatory processes; usually in **body cavities**; **aggressive**
    - **EBV-associated**, (+) B cell markers

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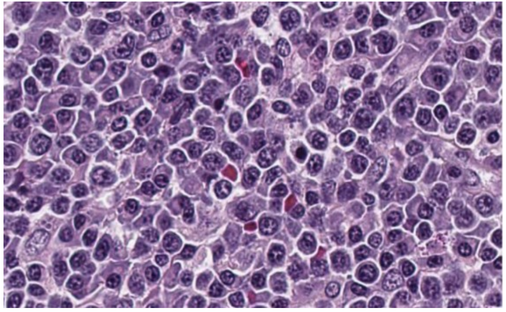
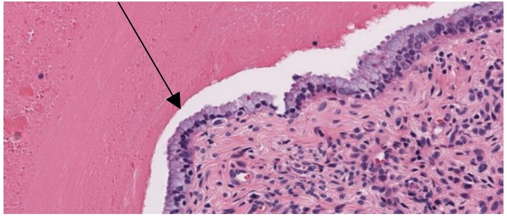
Immunoblastic appearance of PEL

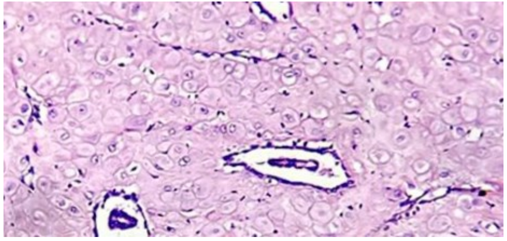


- **Primary Effusion Lymphoma (PEL)**
  - **Large, atypical B cells** with an **immunoblastic appearance** (basophilic cytoplasm, round nucleus with prominent nucleolus, variable pleomorphism)
  - Rare, presents as **effusion without solid tumor mass**
  - Usually, in **immunocompromised** patients; a **poor prognosis**
  - **Positive for HHV8**, often **coinfection with EBV**
  - IHC: (+) CD45, CD30, CD138, EMA, HHV8
    (-) CD19, CD20, PAX5, CD79a (**negative for pan B cell markers**)

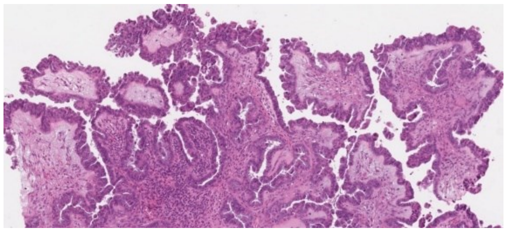
Endocervicosis (endocervical-like epithelium)



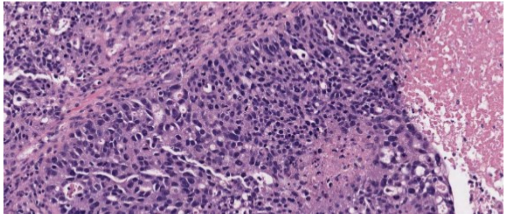
Decidual cells (deciduosis)



Peritoneal serous borderline tumor



Peritoneal high-grade serous carcinoma



MULLERIAN LESIONS OF THE PERITONEUM

- **Mullerianosis**
  - **Endosalpingiosis**: Glands lined by benign **tubal-type (ciliated)** epithelium involving the peritoneum or pelvic/para-aortic lymph nodes; likely secondary as associated with salpingitis
  - **Endometriosis**: Benign endometrial glands and stroma; often accompanying hemosiderin-laden macrophages
  - **Endocervicosis**: Benign endocervical-type epithelium

- **Deciduosis**
  - **Ectopic decidual cells**: Epithelioid with abundant pale pink granular cytoplasm and bland nuclei
  - Arranged individually, in nodules, or in plaques
  - Seen during **pregnancy**; may have associated hemorrhage/inflammation

- **Primary peritoneal serous borderline tumor**
  - **Identical to noninvasive peritoneal implants** of ovarian serous borderline tumors
  - **Diagnosis of exclusion**: Only when the ovaries are uninvolved or with only minimal surface involvement
  - Likely arises from endosalpingiosis, generally **good prognosis**
  - Can get primary peritoneal low-grade serous carcinoma (sample well)

- **Primary peritoneal high-grade carcinoma**
  - **Identical** to the primary tubo-ovarian high-grade serous carcinoma
  - **Diagnosis of exclusion**: Both tubes and both ovaries grossly and microscopically uninvolved (when examined entirely)
  - Diagnosis can only be made at primary surgery prior to any chemotherapy

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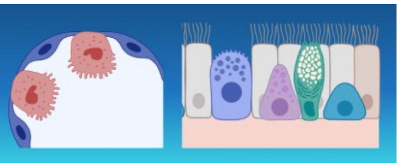
TUMORS OF THE MEDIASTINUM

GENERAL

- **Mediastinum**: Anatomic region located between the lungs, sternum, spine, thoracic inlet, and diaphragm
- About **half of tumors are asymptomatic** and identified incidentally on imaging
- If symptomatic: Cough, pain, dyspnea, **superior vena cava syndrome** (face swelling & distended neck veins due to blockage of SVC)
- Tumors in adults: Carcinoma or lymphoma most common; tumors in children: Leukemia/lymphoma most common

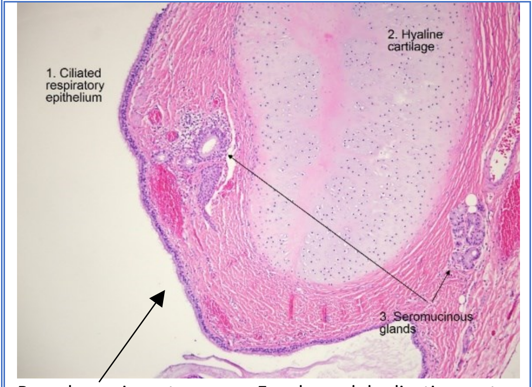
3. PULMONARY PATHOLOGY



DIFFERENTIAL DIAGNOSIS BY LOCATION			
ANTERIOR	**SUPERIOR**	**MIDDLE**	**POSTERIOR**
Thymic tumors Germ cell tumors Thyroid tumors Parathyroid tumors Lymphoma Paraganglioma Hemangioma Lipoma	Thymic tumors Thyroid tumors Lymphoma Parathyroid tumors	Pericardial cyst Bronchial cyst Lymphoma	Neurogenic tumors Schwannoma Neurofibroma Ganglioneuroma MPNST Neuroblastoma Gastrointestinal cyst Bronchogenic cyst

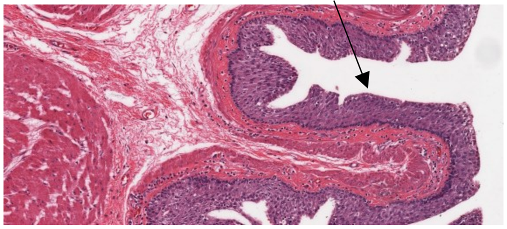
The classic **5 "T's"** of anterior mediastinal masses:

Thymus
Thyroid
Teratoma
Terrible lymphoma
Thoracic aorta (aneurysm)



Bronchogenic cyst

Esophageal duplication cyst



DEVELOPMENTAL CYSTS

- Congenital anomalies that arise during embryogenesis
- **Bronchogenic cyst** (Image courtesy: Chandra Krishnan, MD**)**
  - Well-formed, unilocular cystic structures **resembling bronchus**
  - Contain: **Ciliated epithelium**, **cartilage**, submucosal glands, smooth muscle, and/or degenerative changes
  - Abnormal tracheobronchial tree branching
  - Cured by excision, risk of infection if not excised
  - Hard to distinguish from esophageal duplication cysts if no cartilage ("foregut cyst")
- **Gastrointestinal duplication cyst**
  - Attached to the GI tract, with epithelium that resembles some part of the GI tract and a well-developed double layer of smooth muscle
  - No cartilage (distinguishes from bronchogenic cyst)
  - **Esophageal duplication cyst:** Columnar, squamous, or mixed epithelium
  - **Enteric duplication cyst:** Variable epithelium, usually gastric/duodenal
  - Can contain heterotopic lung or thyroid

Link Link

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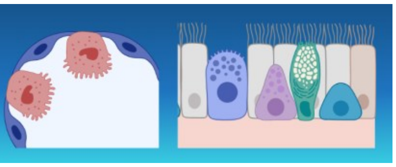
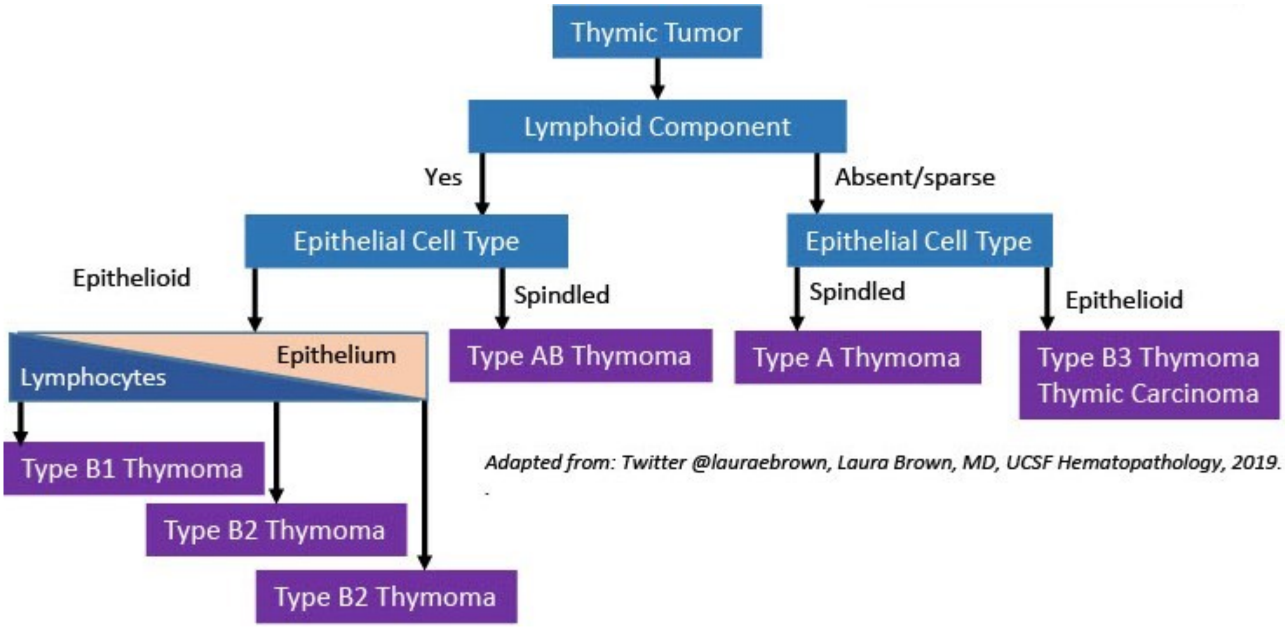
THYMOMA

Type	Composition	Proportion epithelium	Proportion lymphocytes	Prognosis
Type A	Bland spindled to ovoid cells, few or no admixed lymphocytes	Predominant Spindled/oval	Few/none	Excellent
Type AB	Both lymphocyte poor (Type A) and lymphocyte-rich (Type B) components, with a significant proportion of immature T cells	Significant	Significant	Very good
Type B1	Predominantly lymphocytes with dispersed epithelial cells (no clusters)	Low No clusters, polygonal	Predominant	Very good
Type B2	Predominantly lymphocytes, with small clusters of epithelial cells	Low Small clusters	Significant	Fair
Type B3	Predominantly atypical polygonal epithelial cells in sheets	Predominant Epithelioid	Few	Fair, often high stage
Micronodular with lymphoid stroma	Multiple tumors with bland spindled cells surrounded by lymphoid stroma	Significant Spindled	Significant B and T cells No epithelial cells	Excellent
Metaplastic	Biphasic tumor with solid polygonal epithelial cells in a background of bland spindled cells	Predominant Epithelioid/spindled	Few/none	Very good



GENERAL

- Thymic epithelial neoplasms display a **variety of histologic patterns**
  - Heterogeneous and can show multiple patterns of growth; quantify subtype patterns by percentage (%)
  - Care should be taken if attempting to subtype on a small biopsy specimen (likely best diagnosis is "thymoma" and describe the patterns present)
- Overall **rare**, but **most common mediastinal tumor in adults**
- **Multiple subclassifications**, but **stage** is most important prognostically
- Frequent association with **paraneoplastic syndrome** (**myasthenia gravis** most common)
- Immunohistochemistry:
  - Most do not require IHC for subtyping; helpful to differentiate from non-thymus tumors
  - Thymic epithelial cells: (+) AE1/AE3, P63, PAX8, P40
  - T cells in the thymus: (+) CD5, CD3, TdT (immature thymic T cells)


Thymic Tumor
Lymphoid Component
Yes
Absent/sparse
Epithelial Cell Type
Epithelial Cell Type
Epithelioid
Spindled
Spindled
Epithelioid
Epithelium
Lymphocytes
Type AB Thymoma
Type A Thymoma
Type B3 Thymoma
Thymic Carcinoma
Type B1 Thymoma
Type B2 Thymoma
Type B2 Thymoma

Adapted from: Twitter @lauraebrown, Laura Brown, MD, UCSF Hematopathology, 2019.

Bland, oval cells with powdery chromatin

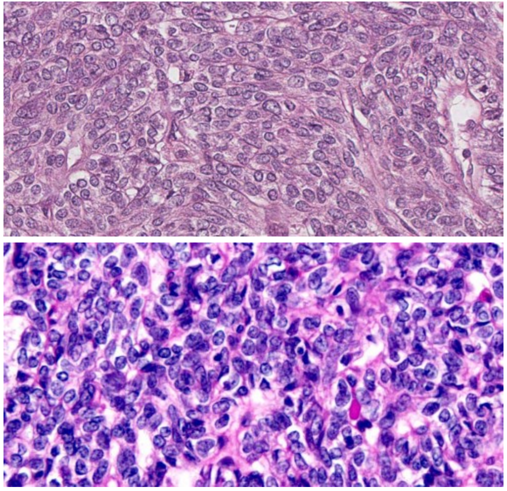


Image credits: Sanjay Mukhopadhyay, MD

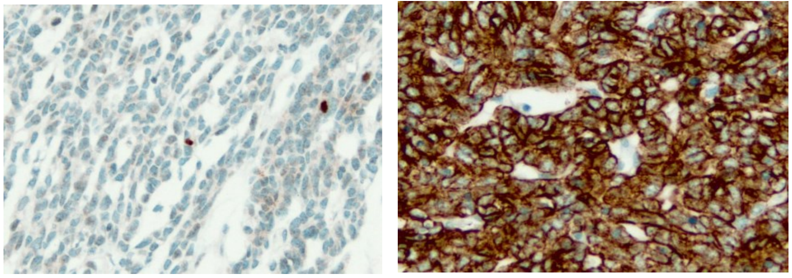
TYPE A THYMOMA

MORPHOLOGY

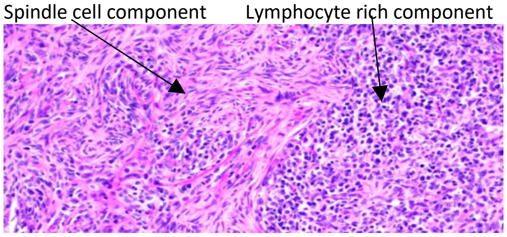
- **Spindled to oval cells** with few or no admixed immature lymphocytes
- Bland nuclei with **powdery chromatin**
- Can have a **microcystic** appearance

OTHER HIGH YIELD POINTS

- Usually **low stage**, often lobulated and **circumscribed**/encapsulated
- **Excellent prognosis**



TdT: No/sparse immature lymphoid cells, CK AE1/AE3 diffusely positive



TYPE AB THYMOMA

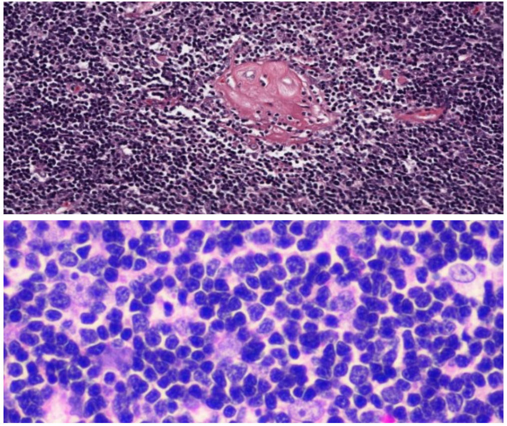
MORPHOLOGY

- **Two components**: lymphocyte-poor spindle cell component and lymphocyte rich component

OTHER HIGH YIELD POINTS

- Varying proportions, but >10% of tumor with moderate infiltrate of immature TdT (+) T cells
- Usually low stage, lobulated, very good prognosis

Resemblance of normal thymus



TYPE B1 THYMOMA

MORPHOLOGY

- **Closely resembles normal thymus**: Dispersed epithelial cells without clusters in a **dense background of immature T cells** mimicking thymic cortex
- Also has areas of medullary differentiation (nodular pale areas, ± Hassall's corpuscles, mostly TdT (+) T cells with numerous B cells)

OTHER HIGH YIELD POINTS

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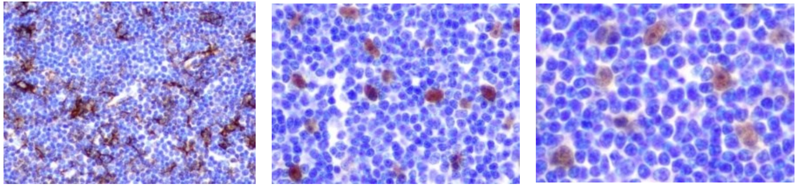
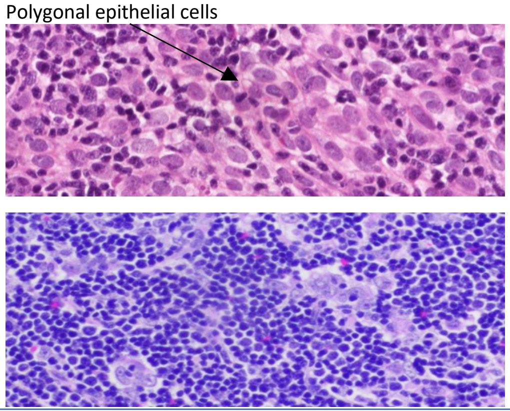
- Usually nodular; **very good prognosis**



CKAE1/AE3, PAX8, P40

Image credits: Kevin Kuan, MD



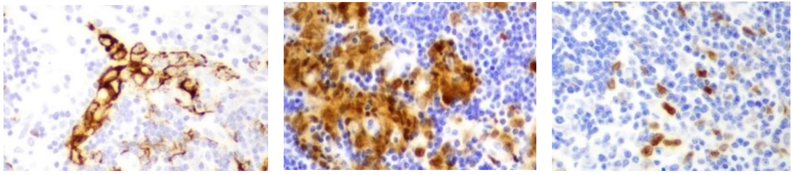
TYPE B2 THYMOMA

MORPHOLOGY

- **Polygonal neoplastic epithelial cells** set in a background of numerous **immature T cells**
- Epithelial cells denser than B1, usually clustered with round vesicular nuclei

OTHER HIGH YIELD POINTS

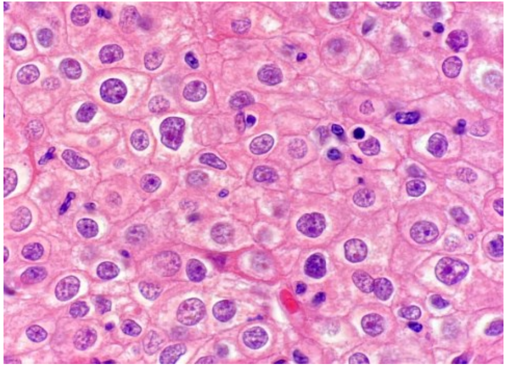
- Often encapsulated, fair to good prognosis



CKAE1/AE3, PAX8, P40

Image credits: Kevin Kuan, MD

Polygonal, pink epithelial cells



Courtesy: Lucas Massoth, MD

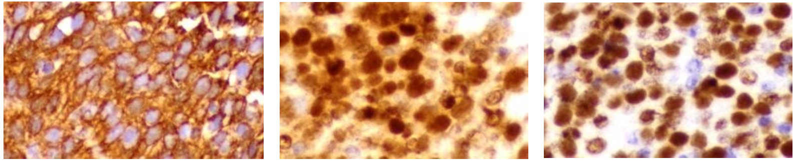
TYPE B3 THYMOMA

MORPHOLOGY

- Mild or moderately **atypical polygonal pink epithelial cells** with lobules of sheet-like or solid growth with fibrous septa; few intermingled T cells

OTHER HIGH YIELD POINTS

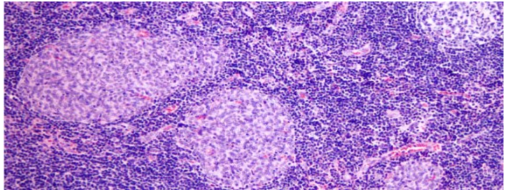
- **Poorly circumscribed** with extension into mediastinal fat/organs
- Most patients have **local symptoms** (chest pain or SVC syndrome)
- Fair prognosis, frequent recurrences



CKAE1/AE3, PAX8, P40

Image credits: Kevin Kuan, MD

Multiple nodules surrounded by lymphoid cells



MICRONODULAR THYMOMA WITH LYMPHOID STROMA

MORPHOLOGY

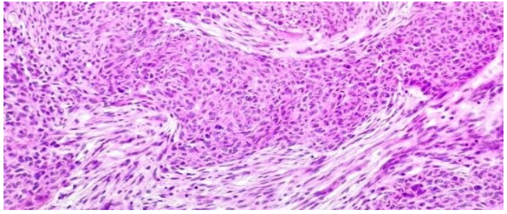
- Multiple epithelial nodules surrounded by prominent lymphoid stroma containing mature B and T cells and devoid of epithelial cells
- May contain germinal centers and/or plasma cells

OTHER HIGH YIELD POINTS

- Excellent prognosis

Image credits: Jake Bledsoe, MD

Bland slender spindle cell component



METAPLASTIC THYMOMA

MORPHOLOGY

- **Biphasic**: composed of alternating areas of solid epithelial cells and bland slender spindle cells
- Absent or very few lymphocytes

OTHER HIGH YIELD POINTS

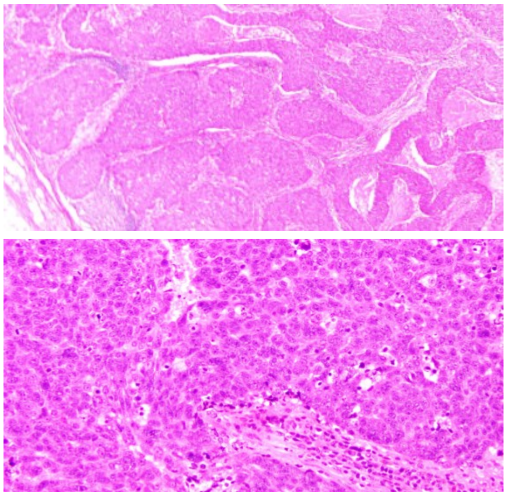
- Very rare, no paraneoplastic syndrome
- **YAP1-MAML2 gene fusions**

Image credits: @Andy_pathology

MISCELLANEOUS THYMOMAS

- **Microscopic thymoma** – Multifocal thymic epithelial proliferations, < 1mm, composed of bland spindled to polygonal cells in well-circumscribed nodules embedded in the medulla or cortex (very rare)
- **Sclerosing thymoma** – Abundant collagen-rich stroma in an otherwise conventional thymoma
- **Lipofibroadenoma** – Benign thymic tumor that resembles fibroadenoma of the breast (very rare)

Resembles conventional carcinomas



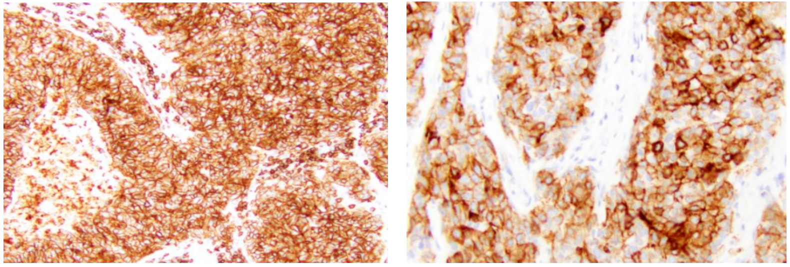
THYMIC CARCINOMA

MORPHOLOGY

- **Malignant** thymic epithelial tumor that lacks thymic organization
- **Resembles conventional carcinomas** in other organs
- Often unequivocal cytologic atypia
- Unencapsulated, no fibrous septa, variable T cell infiltrate

OTHER HIGH YIELD POINTS

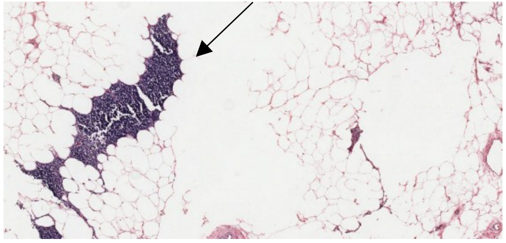
- IHC: (+) AE1/AE3, p63, PAX8, CD5, CD117, Glut1, MUC1



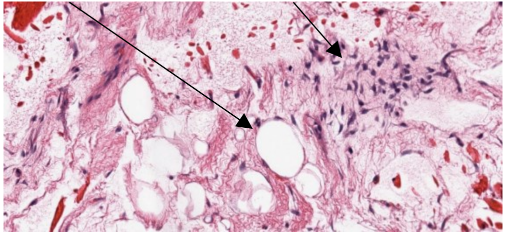
CD5 and CD117. Image credits: Lucas Massoth, MD (@LucasMassoth)

TYPES OF THYMIC CARCINOMA	
Squamous Cell Carcinoma	**Most common**; lacks normal thymic structure; frankly invasive into nearby structures; often eosinophilic cytoplasm and abundant stroma
Basaloid Carcinoma	**High N:C ratio** with cystic/papillary architecture and **peripheral palisading**; numerous mitoses and necrosis; very **aggressive**
Mucoepidermoid Carcinoma	Histologically similar to MEC in other organs; **MAML2 translocation**
Lymphoepithelioma-like Carcinoma	**Poorly differentiated SCC** with rich lymphoplasmacytic infiltrate; often **EBV positive**
Clear Cell Carcinoma	Composed of cells with **vacuolated clear cytoplasm**
Sarcomatoid Carcinoma	Completely or partly spindle cells; if heterologous elements → carcinosarcoma
NUT Carcinoma	Monomorphic round cells with **characteristic abrupt keratinization**, often stain with squamous markers; **NUT gene arrangement**; extremely **aggressive**
Adenocarcinoma	Heterogenous group showing **glandular and/or mucin production**
Undifferentiated Carcinoma	Large cell thymic carcinoma with inflammatory reaction resembling Castleman disease; indolent behavior

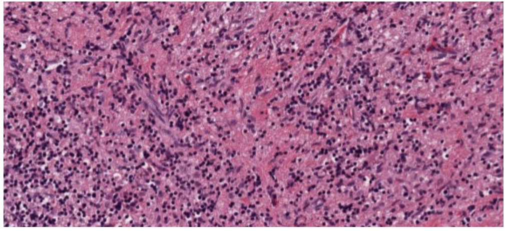
Fibroadipose tissue with entrapped thymic tissue



Mature fat and hyperchromatic spindled cells



Infiltrating fibrosis (sclerosing mediastinitis)

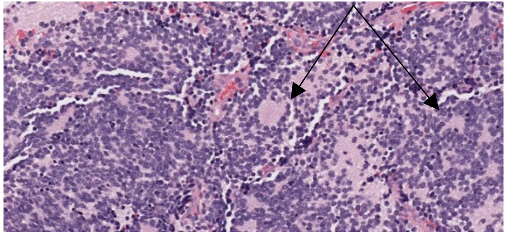


SOFT TISSUE TUMORS/LESIONS

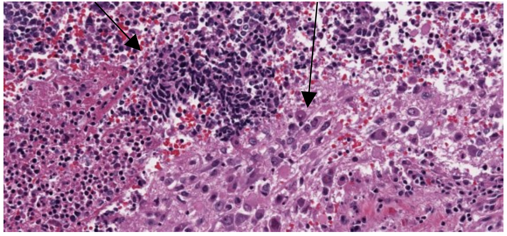
- **Thymolipoma**
  - Encapsulated tumor with mature adipose tissue
  - Interspersed normal thymic tissue
  - Rare, benign, cured with excision
- **Liposarcoma**
  - Most common sarcoma of the mediastinum; poor prognosis
  - Ring or giant marker chromosomes derived from chromosome 12q13
  - MDM2 and CDK4 amplification
  - **Well-differentiated liposarcoma:** variable lipoblasts and hyperchromatic atypical cells in a background of adipocytes and fibrous tissue; morphologic variability
  - **Dedifferentiated liposarcoma:** Well-differentiated liposarcoma component with abrupt transition to an undifferentiated pleomorphic sarcoma
- **Sclerosing (Fibrosing) Mediastinitis**
  - **Non-neoplastic** fibrosis of mediastinum compressing and infiltrating normal structures
  - May be caused by prior infection/response to Histoplasma or TB; IgG4-related disease; autoimmune diseases; or prior radiation
  - Bland spindled cells with lymphoplasmacytic infiltrate ± calcifications
- **Other soft tissue/mesenchymal tumors of the mediastinum:**
  - Synovial sarcoma
  - Solitary fibrous tumor
  - SMARCA4-deficient thoracic sarcoma
  - Angiosarcoma

Link Link

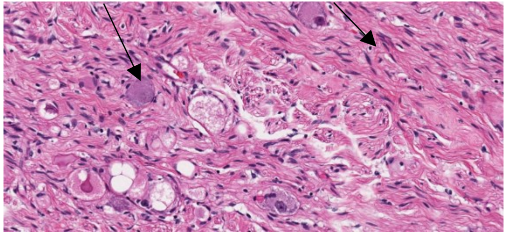
Small round blue cell tumor with pseudorosettes (NB)



Neuroblastoma cells and mature ganglion cells (GNB)



Mature ganglion cells and spindled cells (GN)



NEUROGENIC TUMORS

- **Schwannoma**
  - Biphasic tumor with hypercellular compact areas (Antoni A) and hypocellular cystic areas (Antoni B)
  - Verocay bodies: Rows of nuclear palisading
  - Hyalinized blood vessels, chronic inflammatory infiltrates
- **Malignant peripheral nerve sheath tumor (MPNST)**
  - Spindled cells arranged in sweeping fascicles
  - Densely cellular spindle cells in sweeping fascicles
  - Admixed areas with less cellularity, giving a marble-like effect
  - Geographic necrosis and/or brisk mitotic activity (>10/10 HPF)
- **Neuroblastoma (NB)**
  - Undifferentiated small round blue cell tumor, ± Homer-Wright pseudorosettes, neurofibrillary matrix
  - IHC: (+) Synaptophysin, chromogranin, CD56, neurofilament
- **Ganglioneuroblastoma (GNB)**
  - Intermediate differentiation
  - Composed of both neuroblastic cells (small round blue cells) and ganglion cells (large, mature appearing) in a Schwannian background
- **Ganglioneuroma (GN)**
  - Benign, most mature differentiation
  - Admixed spindled cells and large mature ganglion cells in a fibrillary stroma

Link Link Link Link Link

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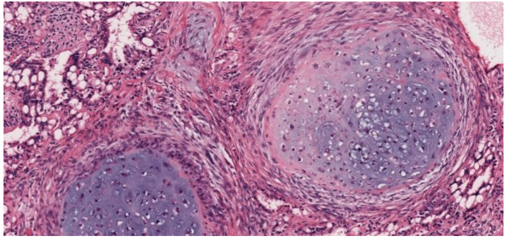
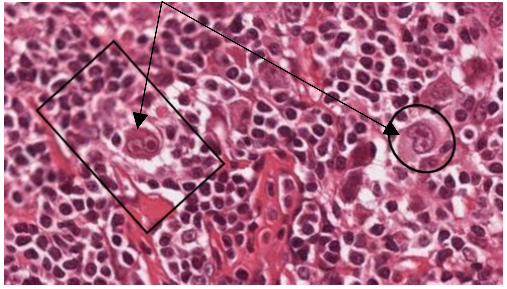
Teratoma with mixture of well-differentiated tissue types



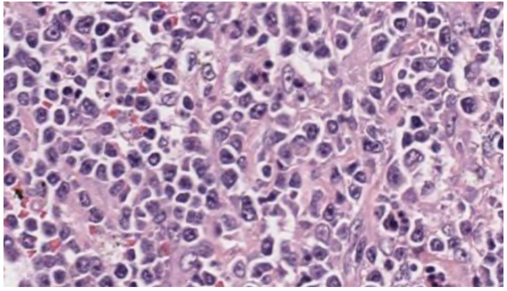
GERM CELL TUMORS

- Associated with Klinefelter syndrome (XXY)
- Morphologically identical to counterparts in the gonads
  - Teratoma – most common mediastinal GCT
  - Seminoma – large polygonal cells with background lymphocytes
  - Yolk Sac Tumor – Schiller-Duval bodies and elevated serum AFP
  - Embryonal Carcinoma – large primitive appearing cells
  - Choriocarcinoma – abundant hemorrhage

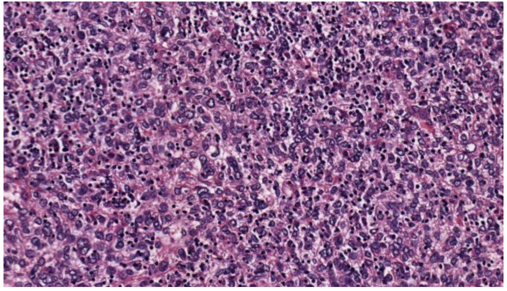
Reed-Sternberg (RS) cells in Classical Hodgkin Lymphoma



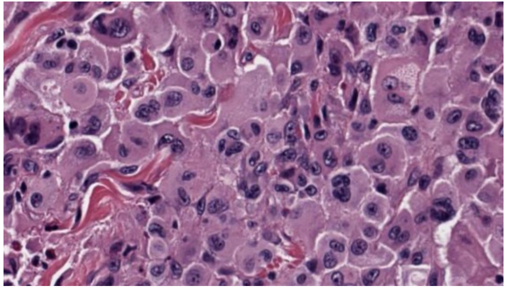
Diffuse growth of large lymphoid cells (DLBCL)



Oval tumor cells, background lymphocytes (FDCL)



Large pleomorphic eosinophilic cells (histiocytic sarcoma)



HEMATOLYMPHOID TUMORS

- **Classic Hodgkin Lymphoma**
  - Most common type of primary mediastinal lymphoma
  - RS cell IHC: (+) CD30, CD15, MUM1, characteristic weak PAX5
    (-) CD20, CD45
- **Primary Mediastinal Large B Cell Lymphoma**
  - Aggressive large B cell lymphoma arising in the mediastinum
  - Diffuse growth of large cells with abundant, often clear cytoplasm
  - Requires clinical exclusion of widespread extrathoracic disease as morphology and IHC identical to DLBCL
- **T Lymphoblastic Leukemia/Lymphoma**
  - Medium-sized cells with scant cytoplasm and fine chromatin; numerous mitoses
  - IHC/Flow: (+) TdT, CD34, CD1a, CD99, CD3
- **Germ Cell Tumor with Associated Hematologic Malignancy**
  - Coexisting clonally related mediastinal germ cell tumor and a hematologic malignancy, which can be systemic or localized
  - Can be any type of heme malignancy, often acute leukemia
  - Very poor prognosis

Link Link Link Link

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HISTIOCYTIC AND DENDRITIC CELL TUMORS

- Follicular Dendritic Cell Lymphoma
- Histiocytic Sarcoma
- Langerhans Cell Histiocytosis

THYMIC NEUROENDOCRINE TUMORS

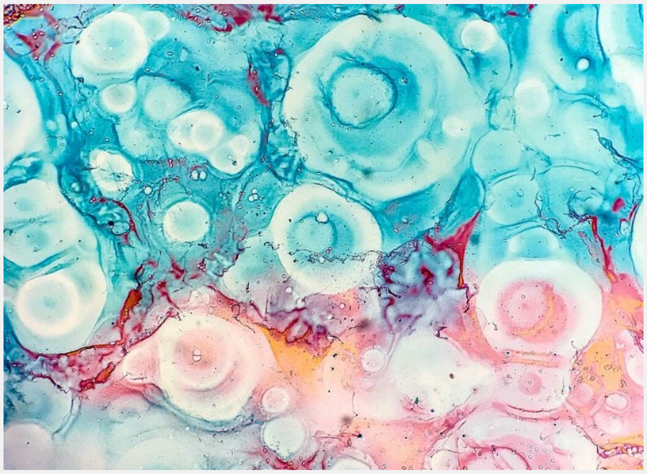
- Rare; classified using the same criteria as in the lung

THYROID AND PARATHYROID TUMORS

- **Thyroid tumors often arise as an extension** from the neck (as opposed to ectopic thyroid tissue)
- Identical histology, IHC, and behavior to the tumor in the neck
- Parathyroid tumors are often formed from **ectopic parathyroid tissue**, usually near the thymus (shared origin – 3rd branchial pouch)

METASTASIS

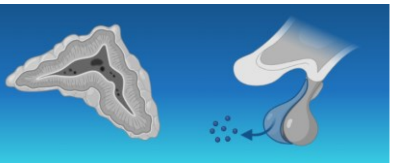
- Always a consideration
- Lung is most common (also consider breast, esophageal, stomach, etc.)


Thick colloid from a Pap-stained FNA of benign thyroid. Image courtesy: Ziad El Zaatari, MD

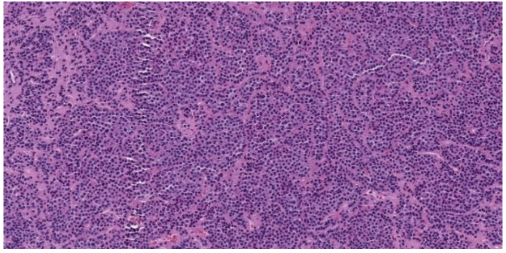
CHAPTER 4: ENDOCRINE PATHOLOGY

Maricel Reyes, MD
Vishwajeeth Pasham, MD
Jared T. Ahrendsen, MD, PhD

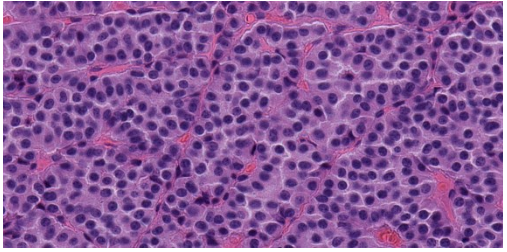
4. ENDOCRINE PATHOLOGY



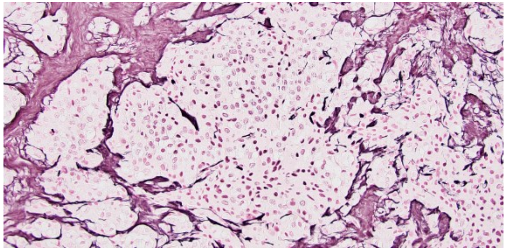
PITUITARY



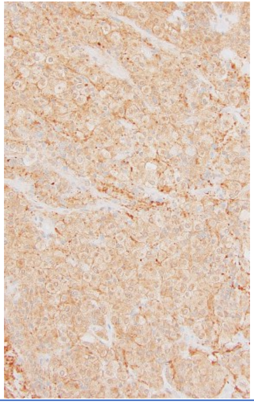
Sheets of monomorphic cells



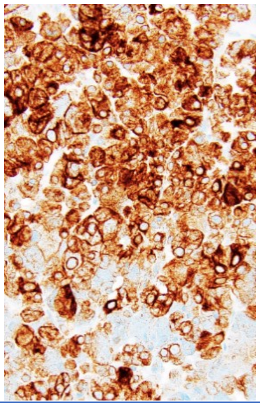
Monomorphic epithelioid neuroendocrine cells



Disrupted reticulin network



Synaptophysin



CAM5.2

PITUITARY ADENOMA

MORPHOLOGY

- Monomorphic neuroendocrine cells with round nuclei
- Cystic structures can be present, particularly in gonadotroph adenomas
- Gonadotroph adenomas can have clear-cell changes and oncocytic changes
- Variety of histologic growth patterns: diffuse, papillary, trabecular
- Can have eosinophilic or basophilic cytoplasm
- Can see perivascular orientation, "endocrine atypia" and occasional mitoses
- Touch prep shows cellular, discohesive, homogenous neuroendocrine proliferation

OTHER HIGH YIELD POINTS

- **Most common tumor of sella** turcica; usually arises in **adults**
- Neoplasm of anterior pituitary hormone-producing cells (adenohypophysis)
- IHC: **(+) synaptophysin**, chromogranin; (-) S100
- **Reticulin** shows dissolution of normal network
- Classification by hormone secretion - typically accomplished by **IHC panel**
- **Functioning adenomas secrete hormones** - often present early with symptoms/tumor syndrome
- Among functioning adenomas, **prolactin secreting adenomas are most common (up to 50% of all adenomas)**; sex variable presentation with females having galactorrhea/amenorrhea and males presenting with sexual dysfunction and mass effect
- ACTH secreting adenomas → **Cushing's disease**
- GH secreting adenomas → **gigantism and/or acromegaly**
- Thyrotroph adenomas are very rare but can present with hyperthyroidism
- Silent adenomas do not secrete hormones, but still stain with hormone IHC
- Gonadotroph secreting adenomas are most often clinically silent
- **Non-functional adenomas typically present with mass effect** – compression of optic chiasm leads to bitemporal hemianopsia, diplopia, and headache
- **Most are sporadic**; minority associated with tumor syndromes
  - MEN1 syndrome, DICER1 syndrome
- Most common genetic defect in sporadic tumors is **GNAS gene mutations**, found in 40% of somatotroph adenomas
- **Benign**, but can invade adjacent structures
- Tumors can grow into cavernous sinuses, anteriorly into sphenoid sinuses, or invade into bone of sellar floor
- Treatment: Trans-sphenoidal resection with option for pharmacotherapy or radiation

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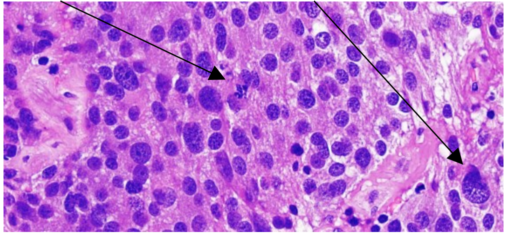


Mitotic activity and nuclear pleomorphism

PITUITARY CARCINOMA

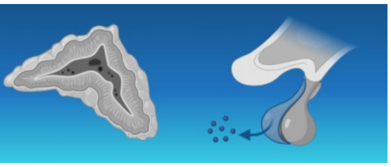
MORPHOLOGY

- **Resemble pituitary adenoma by histology and IHC**
- Generally with more mitoses and higher proliferation index; however, these can be relatively low as well
- There are **no morphologic criteria for pituitary carcinoma**; diagnosis is based on metastasis or non-contiguous intracranial spread

OTHER HIGH YIELD POINTS

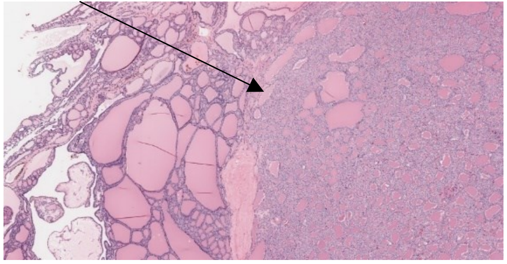
- Very rare; relatively poor prognosis

4. ENDOCRINE PATHOLOGY

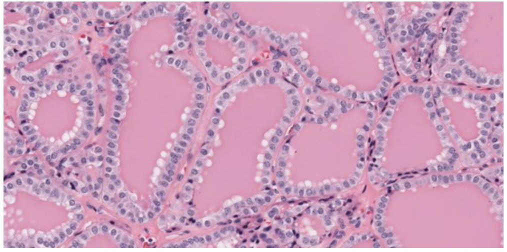


THYROID

Large nodule without distinct capsule



Variably dilated follicles filled with colloid



MULTINODULAR GOITER

MORPHOLOGY

- Gross: **enlarged and nodular exterior surface** with gelatinous cut surfaces, occasional calcifications
- **Large nodules with variably dilated follicles** filled with colloid and lined with low cuboidal epithelium
- **Papillary fronds** with basal nuclei are also present
- May have a pseudocapsule, oxyphilia, nuclear atypia, degenerative changes

OTHER HIGH YIELD POINTS

- **Most common disease of the thyroid gland**; presents as multiple nodules
- **Adults** with a wide age range, more common in **females**
- Majority are **asymptomatic** and with **normal thyroid levels**
- **Iodine deficiency** is most common cause worldwide; **autoimmune** etiology (**Hashimoto's thyroiditis**) most common in USA
- **Increased risk (~3.5%) of thyroid cancer**, predominantly follicular variant of papillary thyroid carcinoma

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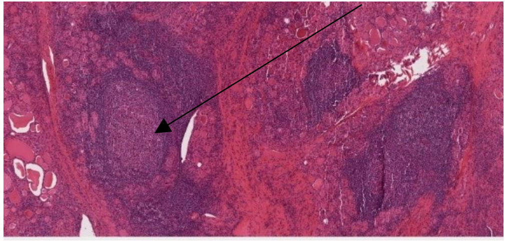
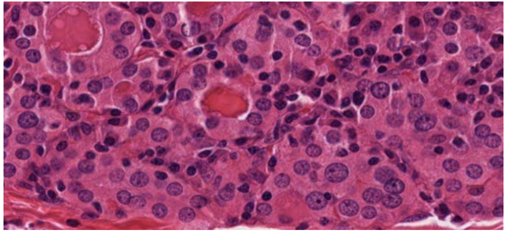
Lymphoplasmacytic aggregates with germinal centers



Hurthle cell metaplasia



CHRONIC LYMPHOCYTIC (HASHIMOTO'S) THYROIDITIS

MORPHOLOGY

- **Gross**: **diffusely enlarged, lobulated thyroid gland** with white cut surfaces
- **Lymphoplasmacytic aggregates** with **germinal centers**, **Hurtle cell** metaplasia, and areas of **fibrosis**

OTHER HIGH YIELD POINTS

- Commonly middle-aged **females**
- Presents as a diffusely enlarged thyroid and variable hyper/hypothyroidism
- May **coexist with other autoimmune diseases**
- **Autoantibodies** to TSH receptor, thyroglobulin, and thyroid peroxidase
- Lab test: Serum antithyroglobulin and antithyroperoxidase (TPO) antibodies
- Increased incidence of lymphoma

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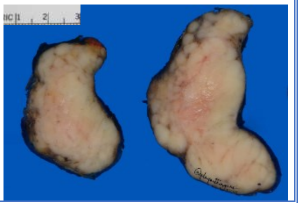
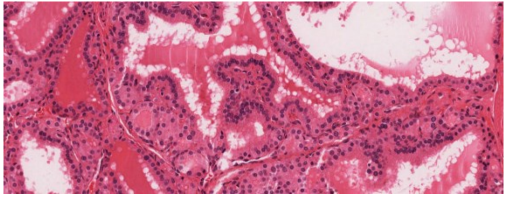


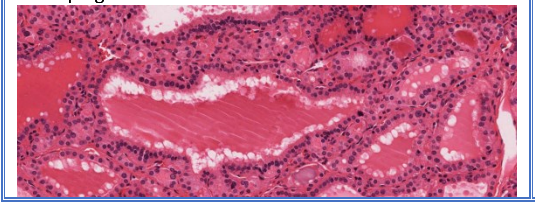
Diffusely enlarged thyroid with white cut surface

Image courtesy of Cory Nash, MS, PA(ASCP)

Papillary infoldings



Scalloping of colloid



GRAVES DISEASE

MORPHOLOGY

- Gross: Diffusely enlarged, beefy red thyroid
- Hyperplastic follicular epithelium with eosinophilic cytoplasm, papillary infoldings, scalloping of colloid, and a patchy lymphocytic infiltrate

OTHER HIGH YIELD POINTS

- Commonly middle-aged **females**
- **Hyperthyroidism** due to circulating anti-TSH receptor antibodies
- Risk factor: High iodine intake
- Labs: Elevated T3 and free T4, decreased TSH
- Associated with polymorphisms in HLA-DR3 and CTLA-4 gene

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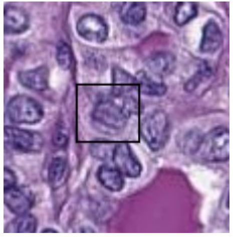
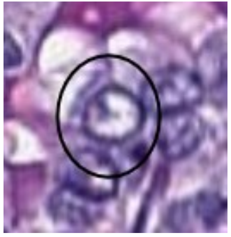
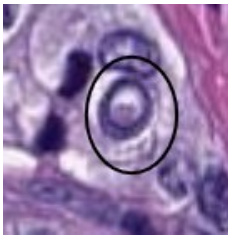
Nuclear groove



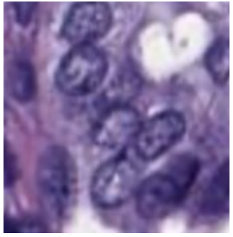
Nuclear clearing



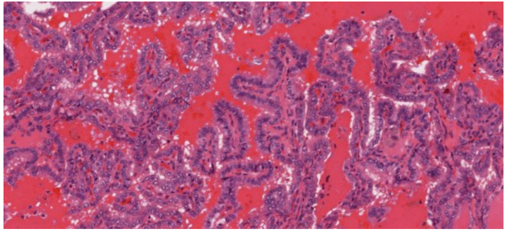
Nuclear pseudoinclusion



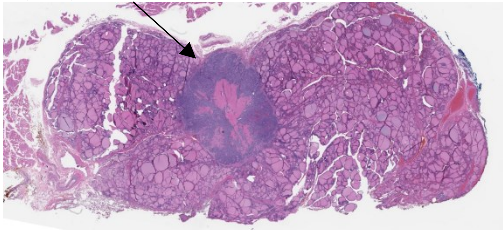
Nuclear overlap



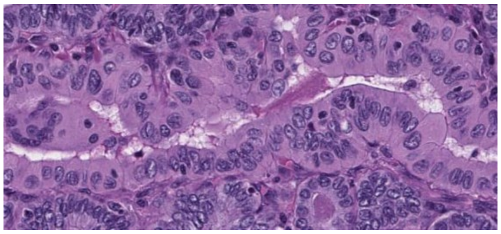
Conventional (classic) PTC with papillae



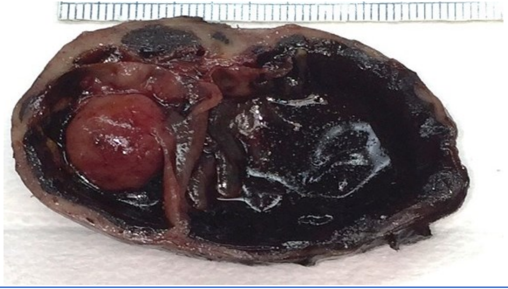
Papillary microcarcinoma (≤1 cm)



Tall cell variant



Gross image of Papillary Thyroid Carcinoma



PAPILLARY THYROID CARCINOMA

MORPHOLOGY

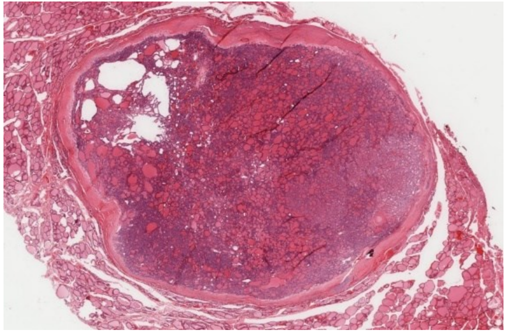
- Gross: **ill-defined mass with infiltrative border**; may have gritty areas corresponding to calcifications
- **Papillary or follicular** architectures are most common
- **Nuclear Features:**
  - Nuclear **enlargement** and elongation
  - Nuclear **overlap**
  - **Irregular nuclear contours**
  - Nuclear **pseudoinclusions**
  - Longitudinal **nuclear grooves**
  - **Chromatin clearing**
- **Conventional (classic) PTC**: Papillary architecture with occasional follicular features; frequent **psammoma bodies**; occasional squamous metaplasia; cystic degeneration; densely eosinophilic colloid
- Histologic Variants:
  - **Papillary microcarcinoma**: ≤1 cm; often missed grossly or incidentally identified; malignant but excellent prognosis
  - **Encapsulated**: Completely surrounded by a fibrous capsule (intact or focally infiltrated); excellent prognosis
  - **Follicular**: Exclusively (or almost exclusively) follicular architecture; can be infiltrative or encapsulated with invasion
  - **Tall cell**: Cells are 2-3x tall as they are wide; abundant eosinophilic cytoplasm; must account for ≥ 30% of tumor; more aggressive
  - **Columnar cell**: Rare; columnar cells with prominent pseudo stratification; lacks conventional nuclear features; resembles endometrioid/intestinal adenocarcinoma; IHC (+) CDX-2
  - **Diffuse sclerosing**: Rare; diffuse involvement with sclerosis and solid nests of tumor cells; background lymphocytic inflammation and psammoma bodies
  - **Cribriform-morular**: Mixture of cribriform, follicular, papillary, trabecular, and solid growth with round squamoid structures (morules); frequent vascular invasion; almost always females; association with FAP (nuclear β-catenin); IHC (+) LEF-1
  - Other variants: Hobnail, solid/trabecular, oncocytic, spindle cell, clear cell, Warthin-like, and PTC with fibromatosis/fasciitis-like stroma
- IHC: (+) TTF-1, thyroglobulin, PAX8, CK7, CK19

OTHER HIGH YIELD POINTS

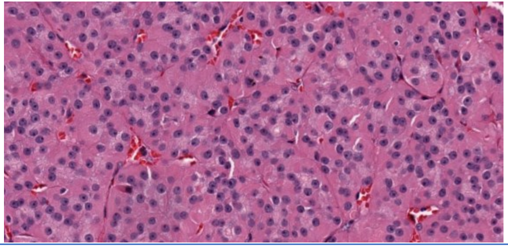
- **Most common type of thyroid cancer** in adults and children
- Usually presents as **painless thyroid nodule** or mass in neck or cervical node, usually cold on scan
- **Female** predilection; often present with **painless thyroid mass**
- Risk factors: **Radiation exposure**, high dietary iodine intake, Carney complex, familial adenomatous polyposis (FAP), presence of benign thyroid disease
- Molecular: **BRAF V600E (most common)**, NRAS, HRAS, KRAS, EIF1AX, TERT, RET gene fusions, copy number alterations
- Prognosis: Overall **excellent prognosis** with a life expectancy similar to general population

Link Link

Path Presenter



Solid, completely encapsulated nodule



Uniform cuboidal cells lacking PTC nuclear features

FOLLICULAR ADENOMA

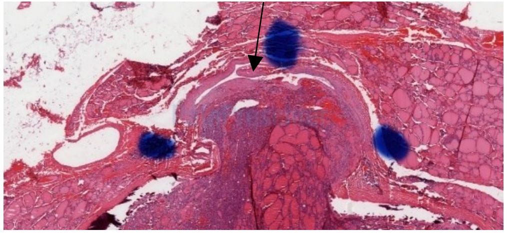
MORPHOLOGY

- Gross: solid encapsulated mass
- **Completely surrounded** by **intact fibrous capsule** (must submit entire capsule to rule out capsular and vascular invasion)
- Cuboidal cells with round, basally located nuclei, **smooth nuclear contours, uniform chromatin** (lacks PTC-type nuclear features, see below)
- Variable architecture but usually one predominant pattern: Microfollicular, macrofollicular, trabecular, insular, spindled, organoid, papillary, etc.
- Variants:
  - Hyperfunctioning – Hyperthyroidism; papillary projections
  - Lipoadenoma – Mature adipose tissue sprinkled throughout
  - Signet-ring cell – Cells with cytoplasmic vacuoles
  - Other variants: Clear cell, spindle cell, black

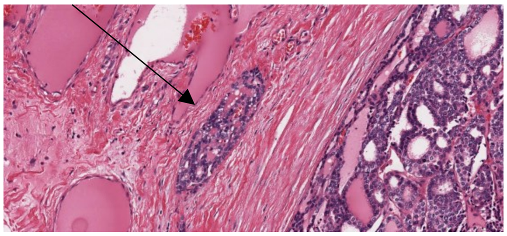
OTHER HIGH YIELD POINTS

- **Benign**; usually presents as a **solitary painless nodule**
- IHC: (+) TTF-1, thyroglobulin, PAX8
- Molecular: **RAS mutations** most common

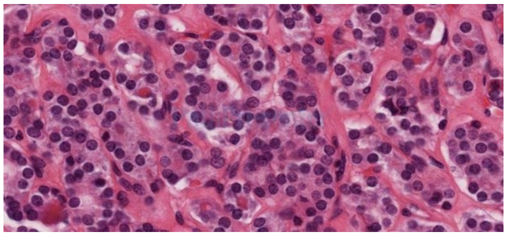
Path Presenter



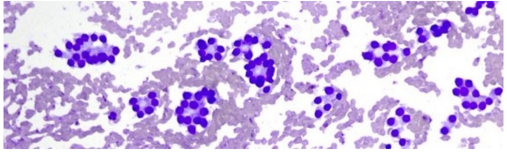
Capsular invasion with mushroom appearance



Vascular invasion



Lacks PTC nuclear features



Cytology: Follicular neoplasm

FOLLICULAR CARCINOMA

MORPHOLOGY

- **Lacks nuclear features of PTC**
- Must demonstrate either **capsular or vascular invasion**; cytologic features are otherwise identical to follicular adenoma
- Often surrounded by a thick capsule:
  - For capsular invasion, must **penetrate the entire capsule**; often with a mushroom appearance
- For vascular invasion, tumor cells must be **adherent to vascular wall** either with **covering endothelium** or **associated with a fibrin thrombus**

OTHER HIGH YIELD POINTS

- Presents as an **asymptomatic/painless mass**
- **Risk factors**: Ionizing radiation, insufficient iodine intake
- **Gross**: **Tan to brown solid** cut surface, can have cystic changes and hemorrhage, permeation of the capsule can be seen grossly
- **Subclassified into 3 groups:**
  - **Minimally invasive** – Capsular invasion only; excellent prognosis
  - **Encapsulated angioinvasive** – Risk of hematogenous metastasis (often bone or lung)
  - **Widely invasive** – Extensive involvement of thyroid and soft tissues, often with prominent vascular invasion
- 4% familial (associations: PTEN hamartoma tumor (Cowden) syndrome, Carney complex)
- IHC: (+) TTF-1, PAX8, thyroglobulin, CK7
- Molecular: **RAS mutations**, **PAX8-PPAR gamma fusion**
- **Poor prognostic factors**: tumor size greater than 4 cm, distant metastases, age greater than 45 years, large size, extensive vascular invasion, extrathyroidal extension

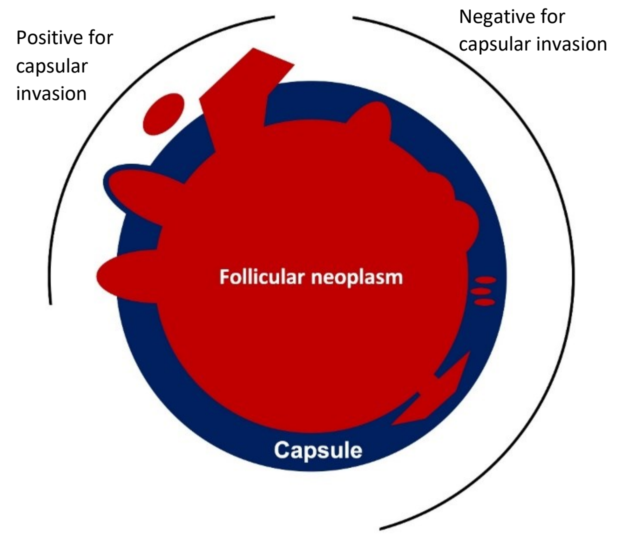
Path Presenter

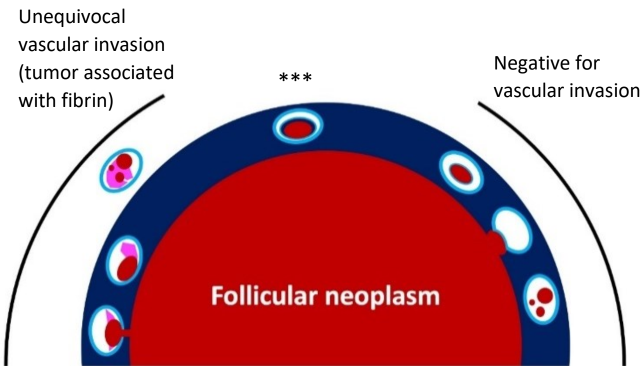
Is that good enough for capsular invasion?

- Most require complete transgression of the capsule; however, some criteria are more lenient
- When in doubt, get multiple deeper tissue levels
- Sometimes, as the tumor grows, it can induce a desmoplastic stromal reaction, inducing a secondar fibrous band:
    - ➢ Look at the gland contour: If the invasive tongue of the tumor extends outside of the usual contour (even if there is a thin capsule), many would consider this invasive

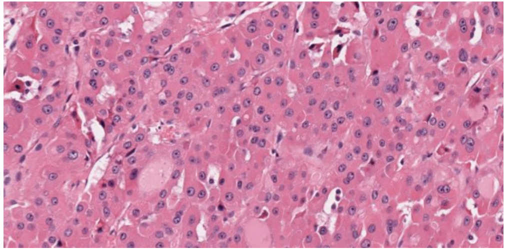
Is that good enough for vascular invasion?

- PTC usually spreads via lymphatics (no RBCs, highlight with D2-40 IHC) to lymph nodes
- Follicular carcinoma spreads via veins (luminal RBCs, use CD31 IHC) hematogenously to lungs/bones
- Vascular invasion must be outside of the tumor: Either in the capsule or beyond
- According to the WHO, tumor cells should be adherent to the vessel wall either with covering endothelium or in a thrombus with fibrin
    - ➢ Newer data suggests that tumor cells within vascular lumina unassociated with a thrombus and tumor cells underlying intact endothelium could represent "pseudoinvasion" given the fenestrated endothelial network of endocrine organs
- Stricter CAP unequivocal definition: invasion of tumor cells through a vessel wall accompanied by fibrin thrombus; correlates more closely with aggressive disease
- *** This example is controversial: WHO criteria say this is sufficient for vascular invasion but stricter CAP criteria would say negative for vascular invasion

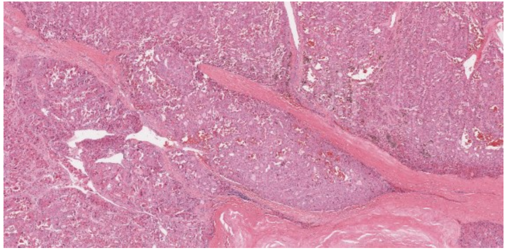

Positive for capsular invasion
Negative for capsular invasion
Follicular neoplasm
Capsule


Unequivocal vascular invasion (tumor associated with fibrin)
***
Negative for vascular invasion
Follicular neoplasm

Hürthle cells: Eosinophilic granular cytoplasm



Capsular invasion in Hürthle cell carcinoma



HÜRTHLE CELL (ONCOCYTIC) TUMORS

MORPHOLOGY

- Neoplasms composed of **oncocytic cells with abundant eosinophilic granular cytoplasm**, central nuclei, and prominent nucleoli
- Oncocytic cells **must comprise >75% of the tumor**; otherwise, you can say "Hürthle cell features"
- Variable architecture: Follicular, trabecular, solid
- **Hürthle cell adenoma:**
    - ➢ Essentially a follicular adenoma composed of Hürthle cells; encapsulated and benign
- **Hürthle cell carcinoma:**
    - ➢ Contains capsular and/or vascular invasion (essentially a follicular carcinoma composed of Hürthle cells)

OTHER HIGH YIELD POINTS

- Worse prognosis and has a greater tendency to extend to soft tissue and have lymph node metastasis than follicular carcinoma
- IHC: (+) TTF-1, thyroglobulin, PAX8, cytokeratin
- Molecular: TP53 and PTEN alterations

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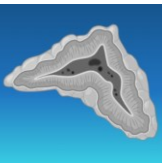
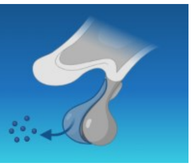



TUMORS OF UNCERTAIN MALIGNANT POTENTIAL

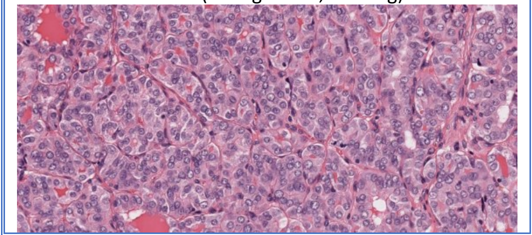
- Some encapsulated neoplasms with follicular architecture can have **questionable capsular/vascular invasion** or **nuclear changes that are mild**, where it is unclear if they are sufficient to justify a diagnosis of papillary thyroid carcinoma
- In such uncertain cases, one can use the diagnosis "**uncertain malignant potential**" (UMP)
  - E.g., tumor cells invade into, but not completely across, the capsule
  - E.g., tumor cells are in a blood vessel, but they are not covered by endothelium or thrombus

- **Follicular Tumor of Uncertain Malignant Potential:**
  - Encapsulated to well-circumscribed follicular-patterned tumor lacking PTC nuclear features with equivocal capsular or vascular invasion (essentially between follicular adenoma and follicular carcinoma)
- **Well-differentiated Tumor of Uncertain Malignant Potential:**
  - Encapsulated to well-circumscribed follicular-patterned tumor with well-developed or partially-developed PTC-type nuclear changes and with questionable capsular or vascular invasion
  - If invasion is completely excluded → NIFTP (see below)

		Capsular/Vascular Invasion		
		Present	**Questionable**	**Absent**
Nuclear features of PTC	**Present**	**Invasive Encapsulated Follicular Variant of PTC**	**Well-differentiated Tumor of Uncertain Malignant Potential**	**Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)**
	Questionable	**Well-Differentiated Carcinoma, NOS**		
	Absent	**Follicular Carcinoma**	**Follicular Tumor of Uncertain Malignant Potential**	**Follicular Adenoma**

Nuclear alteration	Findings
Size & Shape (+1 point)	Nuclear enlargement, overlap/crowding, elongation
Nuclear membrane irregularities (+1 point)	Irregular contours, grooves, pseudo-inclusions
Chromatin characteristics (+1 point)	Clearing with margination, glassy nuclei

PTC nuclear features (enlargement, clearing)



NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES (NIFTP)

MORPHOLOGY

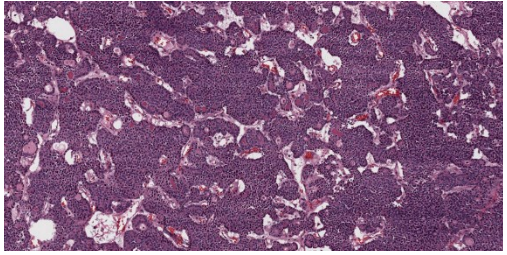
- Diagnostic requirements:
  - **Encapsulated** or clear demarcation
  - Follicular pattern of growth with no true papillae, no psammoma bodies, and <30% solid/trabecular/insular growth pattern
  - Nuclear features of PTC (score of 2-3, see table)
  - No capsular or lymphovascular invasion (submit entire capsule)
  - No tumor necrosis
  - No significant mitotic activity (<3 mitoses/10 high power fields)
- **Nuclear features of PTC are often only partially developed in NIFTP**; if they are very well-developed, consider **BRAF testing** (present in PTC, absent in NIFTP)

Path Presenter

OTHER HIGH YIELD POINTS

- Very low risk of progressive disease
- Treatment with lobectomy alone
- Molecular: **RAS** mutations (like follicular adenoma/carcinoma); **lacks BRAF V600E** mutation (useful to differentiate from PTC)

Insular growth

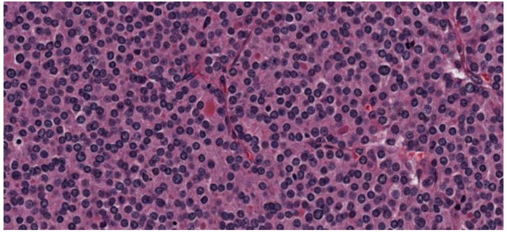


POORLY DIFFERENTIATED THYROID CARCINOMA

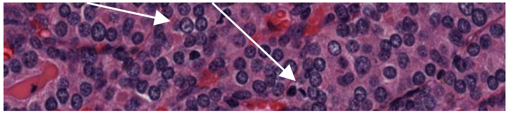
MORPHOLOGY

- **Turin criteria:**
  - Carcinoma of follicular cell origin
  - **Solid, trabecular, or insular growth**
  - Absence of nuclear features of conventional PTC
  - **At least one of the following**:
    - Convoluted nuclei (dedifferentiated PTC nuclear features)
    - ≥3 mitoses / 10 high power fields
    - Tumor necrosis

Small, uniform, hyperchromatic nuclei



Convoluted nuclei, mitoses



- Tumor cells are small, uniform, and hyperchromatic
- Mitoses common; extensive tumor necrosis can give peritheliomatous pattern

OTHER HIGH YIELD POINTS

- Morphology, genetics, and behavior between differentiated carcinoma (i.e. papillary and follicular) and anaplastic carcinoma
- Some arise via dedifferentiation of PTC or follicular carcinoma, while others appear to arise de novo
- Often widely invasive into soft tissues and vessels
- Intermediate prognosis

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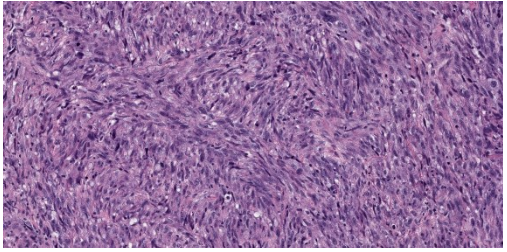
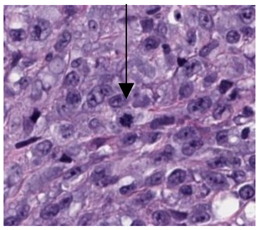
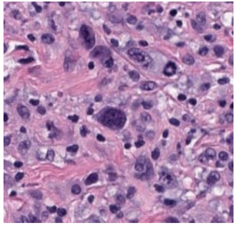
Malignant spindle cells



Mitosis



Nuclear pleomorphism



ANAPLASTIC THYROID CARCINOMA

MORPHOLOGY

- Variable histology with **3 primary patterns:**
  - **Sarcomatoid** – spindle cells resembling pleomorphic sarcoma
  - **Giant cell** – highly pleomorphic cells, some with multinucleation
  - **Epithelial** – squamous nests
- Common findings: **Mitoses, necrosis, invasive growth**
- Often with inflammatory cells

OTHER HIGH YIELD POINTS

- Many seem to arise from dedifferentiation of a pre-existing thyroid tumor (history of long-standing nodule)
- Classically, older women with rapidly growing, firm, fixed neck mass → pain, dysphagia, hoarseness
- IHC: PAX8 usually retained; frequent loss of TTF-1, cytokeratin
- Molecular: Frequent TP53 mutations; also BRAF, PTEN, RAS alterations
- Highly aggressive, very poor prognosis, survival usually < 1 year

Path Presenter

SQUAMOUS CELL CARCINOMA

MORPHOLOGY

- Malignant epithelial tumor with entirely squamous differentiation
- Often extensive infiltration of soft tissue/vessels

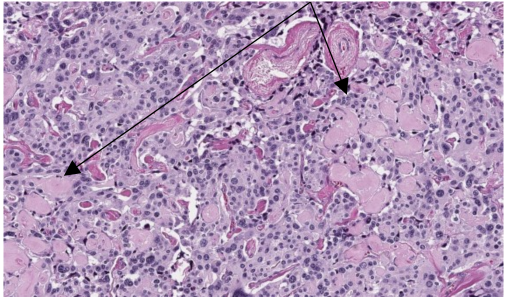
OTHER HIGH YIELD POINTS

- Clinical features and prognosis are similar to anaplastic carcinoma
- Notably, both PTC and anaplastic carcinoma can have areas of squamous differentiation, so the tumor should be sampled well to exclude squamous differentiation of another tumor

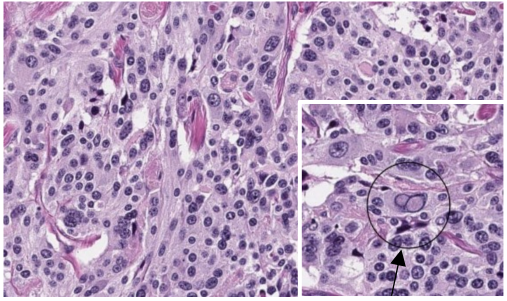
THYROID CARCINOMA IMMUNOHISTOCHEMISTRY

	CK	Thyroglobulin	TTF-1	PAX8	Ki67	P53	Synaptophysin
Normal thyroid follicular cells	+	+	+	+	<3%	**Wildtype**	-
Well-differentiated thyroid carcinoma	+	+	+	+	<10%	**Wildtype**	-
Poorly differentiated thyroid carcinoma	+	-/+	+	+	10-30%	**Mutant**	-
Anaplastic thyroid carcinoma	+/-	-	-/+	-/+	>30%	**Mutant**	-
Medullary carcinoma	+	-	+	+/-		**Wildtype**	+

Neuroendocrine tumor with stromal amyloid



Round nuclei with salt ‘n pepper chromatin



Nuclear pseudoinclusions

MEDULLARY THYROID CARCINOMA

MORPHOLOGY

- Malignant tumor of the thyroid with **parafollicular C-cell** differentiation
- **Wide morphologic spectrum**: Common patterns include solid, lobular, trabecular, and/or insular
- Tumor cells can appear round, spindled, plasmacytoid, or spindled
- Nuclei are **round with speckled “salt ‘n pepper” chromatin**, occasional pseudoinclusions
- Cytoplasm is eosinophilic to amphophilic and granular
- **Frequent stromal amyloid**

OTHER HIGH YIELD POINTS

- Painless neck mass; lymph node involvement common at presentation; **elevated serum calcitonin**
- Mostly sporadic but associated with MEN2A/B (germline RET mutation)
    - In familial tumors, more likely to be multifocal with C-cell hyperplasia
- IHC: **(+) calcitonin (most specific)**, synaptophysin, chromogranin, CD56, TTF-1; (+/-) PAX8; (-) thyroglobulin
- Molecular: **Frequent RET mutations**; occasional RAS mutations
- Intermediate prognosis

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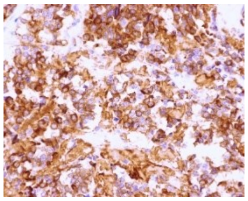
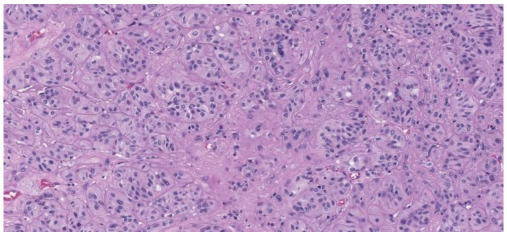


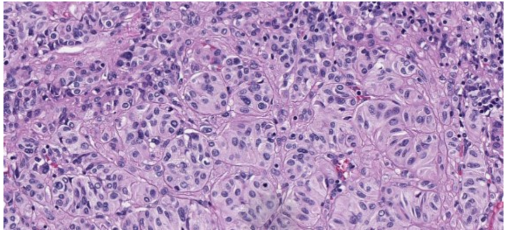
Calcitonin

Image credits: @Patholwalker

Nested architecture



Polygonal cells with granular eosinophilic cytoplasm



HYALINIZING TRABECULAR TUMOR

MORPHOLOGY

- Solid, well-circumscribed nodule
- **Wide trabeculae** and nests separated into **bundles** by stroma
- Large, **polygonal/elongated cells**; eosinophilic **finely granular cytoplasm**; occasional **perinuclear yellow bodies**
- Round nuclei with vesicular chromatin, **frequent nuclear grooves, inclusions, and membrane irregularities** (can be mistaken for PTC on FNA)
- Cells may be enveloped by **hyalinized PAS-d (+) basement membrane material**
- Absence of capsular, vascular, and parenchymal invasion

OTHER HIGH YIELD POINTS

- Rare, follicular derived neoplasm
- IHC: (+) TTF-1, thyroglobulin; (-) calcitonin; **unique membranes staining with MIB1 (Ki67 clone)**
- Excellent prognosis

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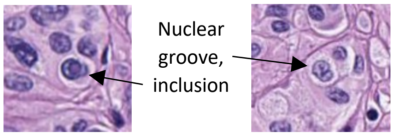
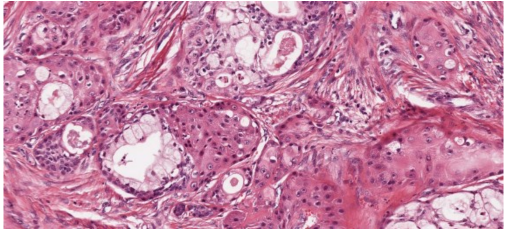


Mucoepidermoid carcinoma



OTHER THYROID TUMORS

- **Mucoepidermoid carcinoma**
    - **Very rare**; favored to represent metaplastic differentiation of follicular derived carcinoma
    - Two cell types: Squamoid cells and mucin-producing goblet cells
    - Occasional MAML2 gene rearrangements
- **Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)**
    - Rare; strong female predilection
    - Consistently associated with **sclerosing Hashimoto’s thyroiditis**
    - Small nests/strands of **epidermoid cells infiltrating sclerotic stroma** with interspersed mucin-secreting cell

SMECE

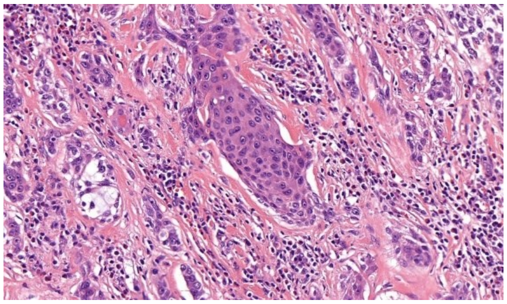


Image credits: Tristan D Rutland MBBS FRCPA (@TristanRutland7)

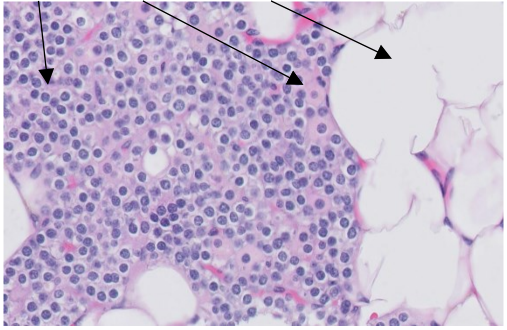
  - Rich inflammatory infiltrate with **prominent eosinophils**
- **Mucinous carcinoma**
  - Malignant; extremely rare
  - Abundant **pools of mucin** with **floating trabeculae/tumor clusters**
  - **Must exclude metastatic mucinous carcinoma**
- **Ectopic thymoma**
  - Typical mediastinal thymoma histology
  - Arises from ectopic thyroid tissue
- **Spindle epithelial tumor with thymus-like differentiation (SETTLE)**
  - Malignant; intermediate behavior
  - Highly cellular; lobulated architecture; spindled epithelial cells that merge into glandular structures
- **Intrathyroid thymic carcinoma**
  - Formerly known as "carcinoma showing thymus-like differentiation" (CASTLE)
  - Identical to thymic carcinoma of mediastinum

OTHER THYROID TUMORS

- Paraganglioma
- Peripheral nerve sheath tumors
- Hemangioma/Angiosarcoma
- Smooth muscle tumors
- Solitary fibrous tumor
- Langerhans cell histiocytosis
- Rosai-Dorfman disease
- Follicular dendritic cell sarcoma
- Diffuse large B cell lymphoma
- MALT lymphoma
- Teratoma
- Metastasis

PARATHYROID

Chief cells, oxyphil cells, and fat



NORMAL PARATHYROID

MORPHOLOGY

- Three main components:
  - **Chief cells:** main cell type; round central nucleus, clear to amphophilic cytoplasm
  - **Oxyphil cells:** large cells with abundant pink cytoplasm
  - **Fat** and fibrous tissue: divides cells into lobules

OTHER HIGH YIELD POINTS

- Regulates calcium levels with parathyroid hormone (PTH)

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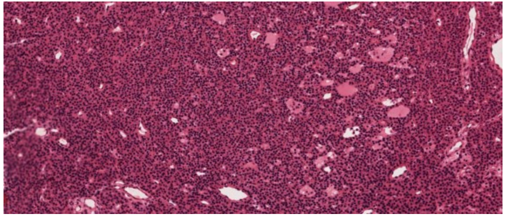
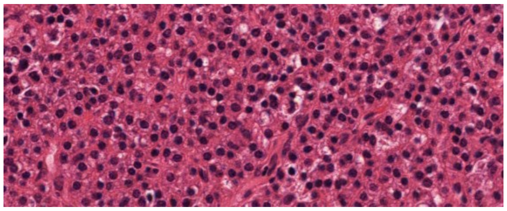
Hypercellular parathyroid without fat



Proliferation of chief cells



PRIMARY PARATHYROID HYPERPLASIA

MORPHOLOGY

- Increased parathyroid cellularity - **usually chief cells** but less commonly oncocytes and clear cells, **no rim of residual normal parathyroid**
- Can have atypia and occasional mitoses; fat is absent

OTHER HIGH YIELD POINTS

- Usually **all four glands** involved but can be asymmetric
- Typically, middle aged females with increased serum PTH and calcium, decreased serum phosphate
- Familial cases associated with **MEN1/2A syndromes**
- **Clinical context is key** in differentiating adenoma vs hyperplasia - look at imaging to see if one markedly enlarged gland or negative localization studies

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Well-circumscribed mass

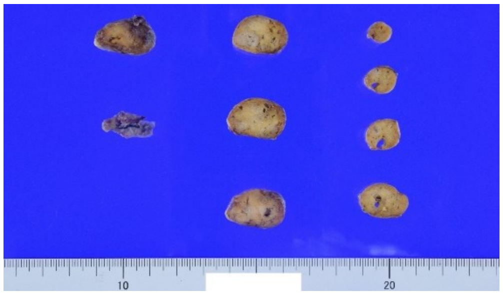
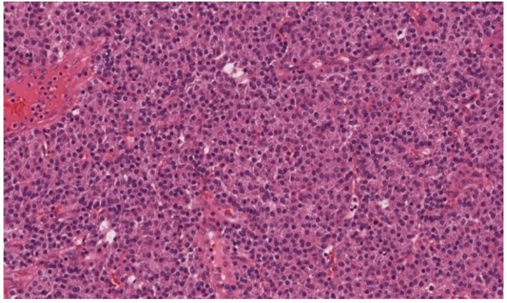


Image credit: Takashi Fujisawa M.D., Ph.D
@Patholwalker

Expanded monomorphic population, no fat present



PARATHYROID ADENOMA

MORPHOLOGY

- **Well-circumscribed**, often encapsulated
- Composed of expanded population of **chief cells (most common)**, oncocytes, or a mixture (uncommon)
- Cells have round, central nuclei with dense chromatin
- Can have follicular architecture; rare mitoses and/or pleomorphism
- Unlike normal parathyroid, **no fat present**

OTHER HIGH YIELD POINTS

- **Benign** encapsulated parathyroid neoplasm; relatively **common**
- Usually involvement is limited to one gland
- Often present with **primary hyperparathyroidism** leading to **hypercalcemia** (metabolic bone disease, kidney stones, fatigue, etc.)
- Minority of cases associated with **MEN1/2A**
- IHC: (+) PTH, GATA3, synaptophysin, chromogranin; **Ki67 <4%**
  (-) TTF-1, thyroglobulin, calcitonin; (+/-) PAX8
- **Many variants** - oncocytic, water-clear cell, lipoadenomas (fat and other parenchymal elements)
- May not be able to distinguish on FNA from follicular thyroid lesions
- Remember to **weigh the specimen**!

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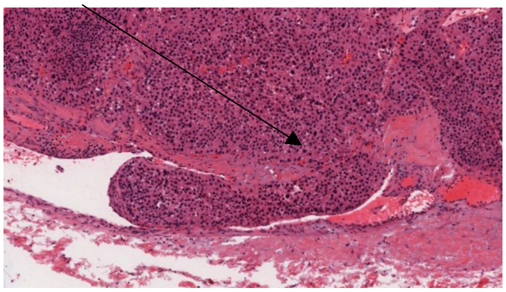
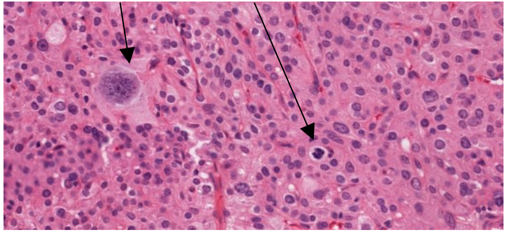
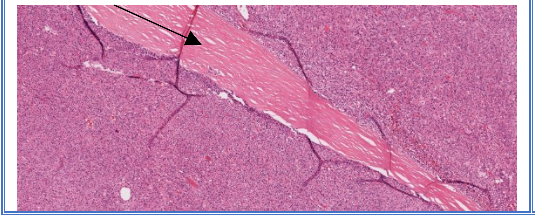
Vessel Invasion



Variable pleomorphism, mitoses



Fibrous band



PARATHYROID CARCINOMA

MORPHOLOGY

- Requires evidence of **one of the following**:
  - **Invasive growth** involving adjacent structures
  - **Invasion of vessels** in capsule or beyond (attached to wall)
  - **Metastases**
- Perineural invasion is a helpful feature; variable pleomorphism/mitoses
- Usually subdivided by broad **fibrous bands**

OTHER HIGH YIELD POINTS

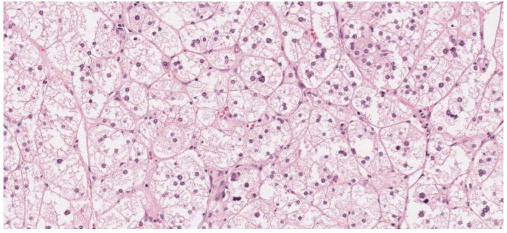
- Rare, malignant neoplasm derived from parathyroid cells
- Usually presents with **hyperparathyroidism** and hypercalcemia
- IHC: (+) PTH, GATA3, synaptophysin, chromogranin; **Ki67 <6-8%**
- Association with **hyperparathyroidism-jaw tumor syndrome** (HPT-JT) - inherited condition with hyperparathyroidism and hypercalcemia
- **"Atypical Parathyroid Adenoma"**
  - Adenomas that exhibit some features of parathyroid carcinoma but **lack unequivocal invasive growth**
  - **Frequent findings**: fibrous bands, adherence to adjacent structures, tumor within capsule, solid/trabecular growth, nuclear atypia, increased mitoses
  - Usually, benign clinical course with close follow up

Path Presenter

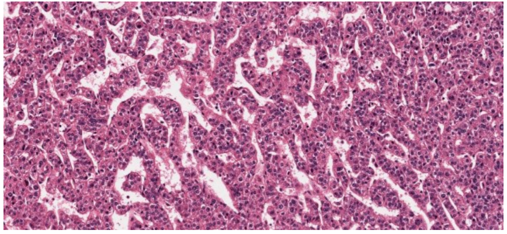
ADRENAL

ADRENAL CORTICAL ADENOMA

Nests of lipidized (clear) tumor cells



Cords of lipid-poor (pink) tumor cells



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MORPHOLOGY

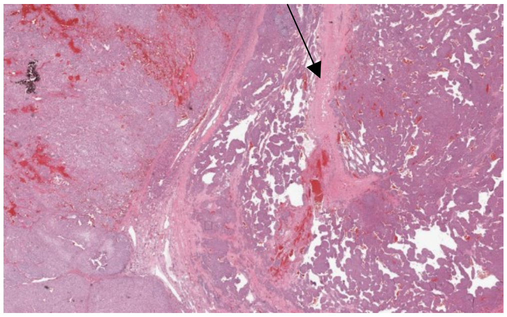
- Gross: circumscribed **golden yellow mass**
- Tumor cells can be lipid-rich (clear) or lipid-poor (pink), arranged in nests & cords separated by abundant vasculature
- Occasional lipofuscin pigment
- Nuclei are generally small and round but extreme “endocrine atypia” can be encountered
- Low to absent mitotic activity
- “Spironolactone bodies” (spherical eosinophilic structures) in aldosterone secreting adenomas treated with spironolactone

OTHER HIGH YIELD POINTS

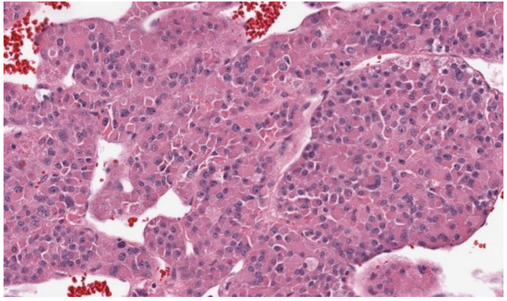
- Benign, very common, often incidental and unilateral
- On a spectrum and may be difficult to differentiate from hyperplastic nodules (more often multifocal and bilateral)
- IHC: (+) SF1, inhibin, Melan-A, calretinin, synaptophysin
  (-) chromogranin, cytokeratin, S100
- Associated with MEN1, FAP, Carney Complex, Beckwith-Wiedemann
- Can be non-functional (85%) or functional (15%)
  - **Aldosterone** producing → **Conn syndrome:** hypertension and hypokalemia
  - **Cortisol** producing (ACTH-independent) → **Cushing syndrome:** central obesity, moon facies, hirsuitism, poor healing, striae
  - **Sex-hormone** producing (rare, more common in carcinoma) → virilization or feminization depending on patient’s sex

ADRENAL CARCINOMA

Varied architecture with fibrous bands



Large nests of oncocytic tumoor cells



MORPHOLOGY

- Gross: lobulated, large tumors that are yellow, orange, tan, or brown with cystic change, hemorrhage, and/or necrosis
- Solid, broad trabeculae or large nested growth (larger nests than adenoma)
- Thick fibrous capsule with occasional fibrous bands
- Frequent tumor necrosis, vascular or capsular invasion, and increased mitotic activity
- Variants: oncocytic, myxoid, sarcomatoid

OTHER HIGH YIELD POINTS

- Malignant, more common in older adults
- Can present as an incidental unilateral mass or with an endocrinopathy
- Mostly sporadic but can be associated Li Fraumeni

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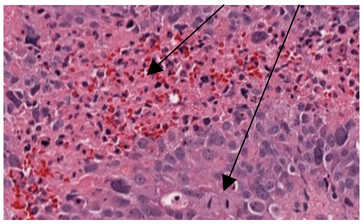
Necrosis, mitoses



Lobulated tumor with tan-brown cut surface

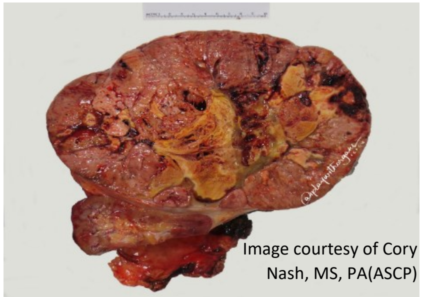


Image courtesy of Cory Nash, MS, PA(ASCP)

DISTINGUISHING BETWEEN ADRENOCORTICAL ADENOMA AND CARCINOMA

WEISS CRITERIA

- Most widely used system but doesn't work well with borderline cases or variants
- Presence of **≥3 criteria correlate with malignant behavior**
- Cannot be used for oncocytic adrenal neoplasms or pediatric adrenal tumors (see below)
- Features only seen in metastasizing tumors:
    - ≥6 mitoses per 50 high power fields
    - Atypical mitoses
    - Invasion of venous structures

"MODIFIED" WEISS CRITERIA

- Designed to be more reproducible
- Total score of **3 or greater** correlated with malignant behavior

RETICULIN ALGORITHM

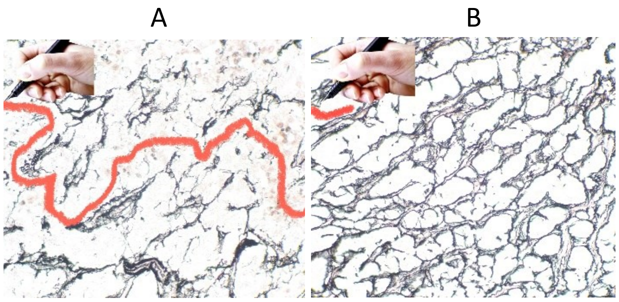
- Check intactness of reticulin network; **if intact throughout** → adenoma; if disrupted, then:
- **Malignancy is identified by at least one of the following:**
    - Tumor necrosis
    - High mitotic rate (>5/50 HPF)
    - Venous invasion

Although distinction between adenoma and carcinoma is usually straight forward, in some borderline cases, it may be more appropriate to categorize as "**Uncertain Malignant Potential**"

Although not fitting into the above schemes, Ki67 can be helpful, too. The proliferation index in adenomas is usually <5% whereas carcinomas tend to have a proliferation index >5%.

WEISS CRITERIA (≥ 3 = MALIGNANT)
High nuclear grade (based on Fuhrman criteria)
Mitotic rate >5 per 50 high power fields
Atypical mitotic figures
<25% clear cells
Diffuse architecture
Tumor necrosis
Venous invasion
Sinusoidal invasion
Capsular invasion

"MODIFIED WEISS CRITERIA	POINTS
Mitotic rate >5 per 50 HPF	2
<25% clear cells	2
Atypical mitotic figures	1
Tumor necrosis	1
Capsular invasion	1



Reticulin stain in Adrenocortical carcinoma, Squiggle sign (A) vs normal staining pattern (B):, image courtesy: Matthew Zaborowski, MD (@Mattzaborowski1)

Lu-Weiss-Bisceglia Criteria	
Major criteria	>5 mitoses per 50 HPF
	Atypical mitotic figures
	Venous invasion
Minor criteria	Size >10 cm and/or weight >200 grams
	Tumor necrosis
	Sinusoidal invasion
	Capsular invasion

ONCOCYTIC ADRENOCORTICAL NEOPLASMS

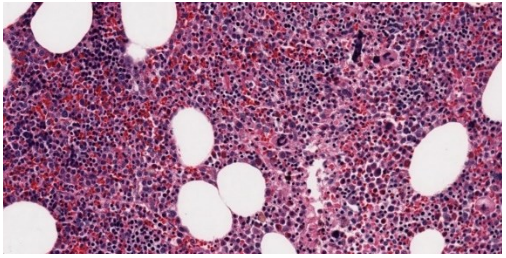
MORPHOLOGY

- Cells with abundant granular eosinophilic cytoplasm
- >90% of tumor to be considered oncocytic
- Often with areas of nuclear pleomorphism, intranuclear pseudoinclusions, and prominent nucleoli

OTHER HIGH YIELD POINTS

- Mostly non-functional
- Cannot use Weiss criteria, use **Lu-Weiss-Bisceglia Criteria** instead
    - **1 major criteria → Malignant carcinoma**
    - **1-4 minor criteria → Uncertain malignant potential**
    - **No major and minor criteria → Benign adenoma**

Hematopoietic tissue and adipose tissue



MYELOLIPOMA

MORPHOLOGY

- Composed of **mature fat** and **bone marrow elements**

OTHER HIGH YIELD POINTS

- Benign; second most common adrenal neoplasm
- Often older adult presenting with incidental asymptomatic mass
- Can often diagnose on imaging due to fat content

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Oval mass with gray cut surface and areas of hemorrhage

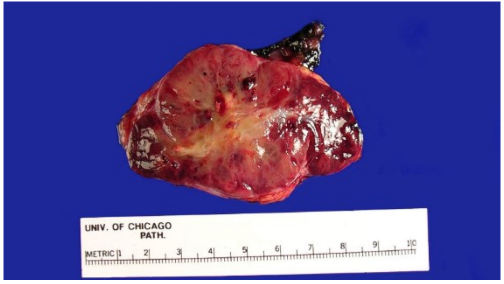
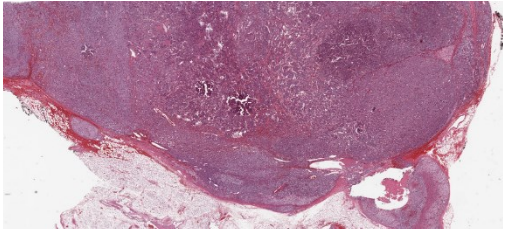
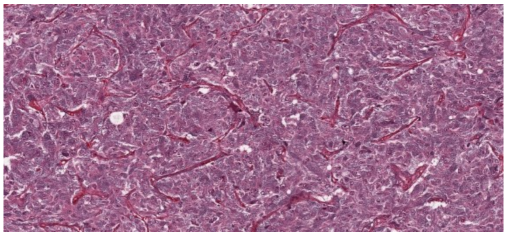


Image credits: Cory Nash, MS, PA(ASCP), Dept. of Pathology, University of Chicago; Used with permission.

Sharply circumscribed mass



Nested “Zellballen” architecture



PHEOCHROMOCYTOMA

MORPHOLOGY

- Gross: unicentric round/oval mass, sharply circumscribed with gray-white cut surfaces and areas of hemorrhage
- Classically, **nested (“Zellballen”) architecture**; can also show trabecular or diffuse growth
- Polygonal cells with amphophilic to purple cytoplasm
- **Richly vascular**, often with hemorrhage and/or hemosiderin
- Frequent **intranuclear pseudoinclusions** and **intracytoplasmic hyalin globules** (PASD+)
- Nuclear pleomorphism can be prominent but mitotic figures are rare

OTHER HIGH YIELD POINTS

- Tumor of chromaffin cells that arises from **adrenal medulla**
- All are **malignant** but only **~10% metastasize**
  - No current standardized test to assess tumor risk
- Can occur at any age but usually adults
- ~50% are asymptomatic and discovered incidentally
- Can make **catecholamines**
  - Hypertension, headache, tachycardia, sweating
  - Sustained or paroxysmal symptoms
  - Can detect in urine or serum metanephrine testing
- IHC: **(+) diffuse chromogranin** and synaptophysin, **sustentacular S100** and SOX10; (-) cytokeratins, SF1, inhibin, Melan-A, calretinin
- **At least 30% are familial due to germline mutations** (genetic testing is recommended for all patients)
  - Common mutations: SDH, RET, NF1
  - Higher risk of metastasis with SDHB mutations
- Complete resection is only cure; can have metastasis many years later

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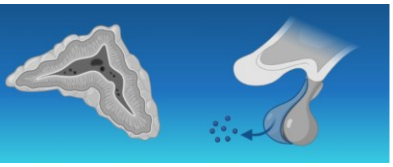
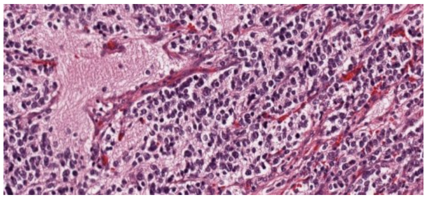
PARAGANGLIOMA

- Arise from **extra-adrenal paraganglia**, but **morphologically and functionally like pheochromocytoma** (also frequently hereditary!)
- **Head and neck paragangliomas:**
  - Arise from parasympathetic nerves
  - Most common sites: carotid body and jugulotympanicum
- Generally non-functional and good prognosis (<5% risk of metastasis)
- **Sympathetic paragangliomas:**
  - Arise from vertebral and paravertebral sympathetic chains and sympathetic nerves (mainly in the abdomen)
  - Frequently functional
  - Risk similar to pheochromocytoma; SDHB mutation associated with increased risk of metastasis
- **Composite paraganglioma:**
  - Rare
  - Combined with ganglioneuroma, ganglioneuroblastoma, neuroblastoma or peripheral nerve sheath tumor
  - Most common locations: adrenal, urinary bladder and retroperitoneum

4. ENDOCRINE PATHOLOGY



NEUROBLASTOMA



MORPHOLOGY

- Small round blue cells +/- rosettes
- Neurofibrillary matrix without Schwannian stroma
- Most primitive/aggressive
- Malignant

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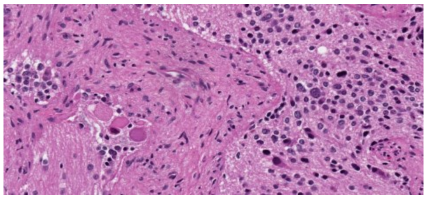
GANGLIONEUROBLASTOMA



MORPHOLOGY

- Small round cells (neuroblastoma) intermixed with Schwannian stroma, including ganglion cells
- Intermediate differentiation
- Malignant

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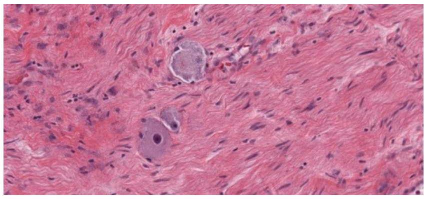
GANGLIONEUROOMA



MORPHOLOGY

- Ganglion cells set in abundant fibrillary Schwannian stroma
- No neuroblastoma or neuropil
- Most mature
- Benign

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OTHER HIGH YIELD POINTS

- Derived from neural crest cells → sites reflect path of migration → **adrenal gland is most common** followed by abdominal ganglia, thoracic ganglia, and pelvic ganglia
- Neuroblastoma is **3rd most common pediatric tumor** (after leukemia and brain tumors)
- Most common neoplasm in first year of life; ~**90% occur within the first 5 years of life**
- Neuroblastoma IHC: (+) synaptophysin, chromogranin, PGP9.5, CD56, NB84, PHOX2B
- Ganglioneuroma IHC: Schwann cells (+) S100; Ganglion cells (+) synaptophysin, neurofilament
- **Favorable versus unfavorable histology** is determined by age, degree of neuroblast differentiation, nodular pattern, degree of Schwannian stromal development, and mitotic-karyorrhexis index (MKI)
- Molecular genetics:
    - **MYCN is a major oncogenic driver; amplification → higher risk**
    - Whole chromosome copy number gains without structural abnormalities **(hyperploidy) have an excellent prognosis**

COMPOSITE PHEOCHOMOCYTOMA/PARAGANGLIOMA

MORPHOLOGY

- A pheochromocytoma or paraganglioma combined with a developmentally related neurogenic tumor such as ganglioneuroma, ganglioneuroblastoma, neuroblastoma, or peripheral nerve sheath tumor

OTHER HIGH YIELD POINTS

- Each component looks and stains like it would by itself
- Can occur in the setting of NF1
- If surgically resected, good prognosis

FAMIAL ENDOCRINE TUMOR SYNDROMES

Multiple Endocrine Neoplasia (MEN) 1 & 2

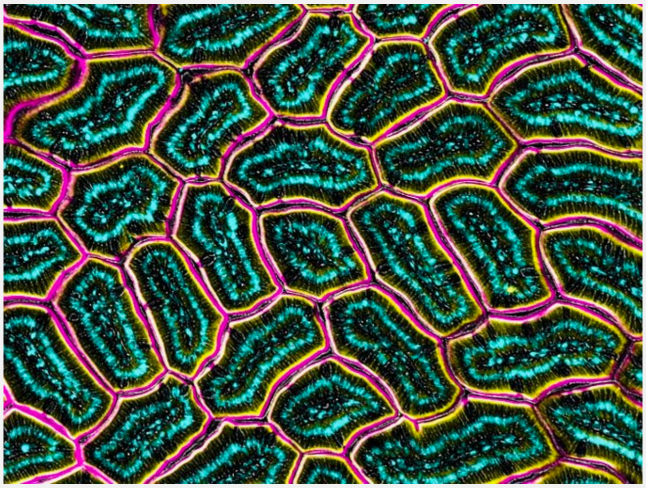
	MEN1	MEN2A	MEN2B
Gene	Menin, autosomal dominant	RET, autosomal dominant	RET, autosomal dominant
Most common conditions	**P**arathyroid hyperplasia **P**ituitary adenoma **P**ancreatic/duodenal neuroendocrine tumor *Think "3 P's"*	**P**arathyroid hyperplasia **P**heochromocytoma **M**edullary thyroid carcinoma *Think "2 P's, 1 M"*	**P**heochromocytoma **M**edullary thyroid carcinoma **M**ucosal neuromas **M**arfanoid features *Think "1 P, 3 M's"*
Other conditions	Adrenal cortex, thymus, lungs, stomach tumors	Hirschsprung disease	Ganglioneuromas

Often multiple tumors in each organ (e.g., diffuse pancreatic microadenomatosis with several larger dominant nodules)

Familial Paraganglioma-Pheochromocytoma Syndromes

- Caused by mutations in genes encoding subunits of **succinate dehydrogenase (SDH)**
- Autosomal dominant; can see mutations in SDHA, **SDHB (most common)**, SDHC, SDHD, or SDHAF2

- Immunoreactivity for SDHB is lost in SDH-deficient tumors caused by mutations any of the subunits → can be used to screen for SDH mutations in paragangliomas, pheochromocytomas, and unusual GISTs and RCCs
- **Most common tumor: paraganglioma/pheochromocytoma**, can be multifocal
- Tumors associated with SDHB mutations are often more aggressive and present at a younger age
- Other specific tumors:
    - **SDH-deficient Gastrointestinal Tumor (GIST)** – usually occurs in kids or young adults; epithelioid morphology and can be multifocal or plexiform; metastasize to lymph nodes; not responsive to RTK inhibitor therapy (no CKIT mutations!); overall more indolent
    - **SDH-deficient Renal Cell Carcinoma (RCC)** – eosinophilic cytoplasm with "flocculent" cytoplasm/inclusions; neuroendocrine-like nuclei (round, evenly dispersed chromatin, solid to nested architecture); young age and good prognosis
    - **Carney Triad** – generally non-hereditary SDHC promoter hypermethylation; paraganglioma + SDH-deficient GIST + pulmonary chondroma
    - **Carney-Stratakis Syndrome** – paraganglioma + SDH-deficient GIST



Fluorescence microscopy, intestinal villi. Image courtesy: Amy Engevik, MD

CHAPTER 5: GASTROINTESTINAL PATHOLOGY

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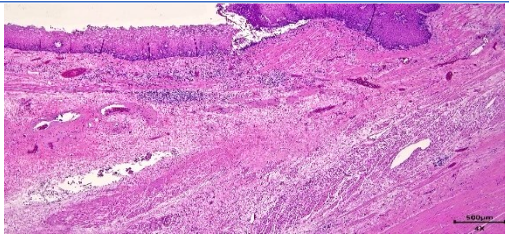
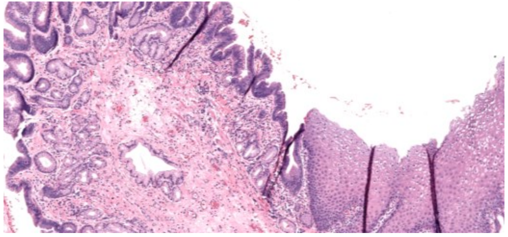
Binny Khandakar, MD
Aastha Chauhan, MD

5. GASTROINTESTINAL PATHOLOGY

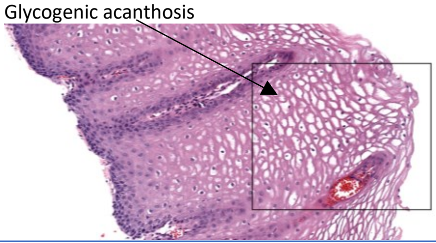
ESOPHAGUS



Heterotopic gastric mucosa (Inlet patch)



Glycogenic acanthosis



NORMAL HISTOLOGY

STRUCTURE

- **Mucosa:** Non-keratinizing stratified squamous epithelium with underlying lamina propria and muscularis mucosae
- **Submucosa**: Loose connective tissue containing blood vessels, lymphatics, mucous glands, nerve fibers, and ganglion cells; submucosal glands are connected to the lumen by squamous epithelium-lined ducts
- **Muscularis propria:** Inner circular and outer longitudinal layer of smooth muscles, and myenteric plexus
- **Adventitia:** Loose connective tissue
- **Squamocolumnar junction/Z-line** is the mucosal junction of squamous and columnar epithelium whereas **gastroesophageal junction (GEJ)** between the tubular esophagus and proximal stomach is marked by rugal folds

BENIGN INCIDENTAL FINDINGS

- **Gastric inlet patch**: Heterotopic gastric mucosa in the upper 1/3rd of the esophagus
- **Pancreatic metaplasia/heterotopia**: Benign pancreatic acini and ducts
- **Glycogenic acanthosis**: Epithelial hyperplasia with abundant glycogen accumulation in the superficial squamous cells; endoscopic appearance of solitary/scattered white plaques; extensive involvement of the esophagus may be a manifestation of **Cowden syndrome**

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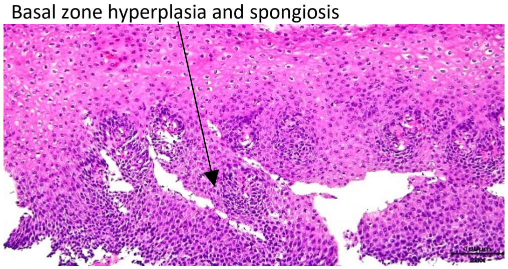
INFLAMMATORY/NON-NEOPLASTIC CONDITIONS

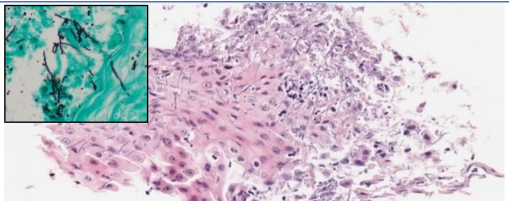
Basal zone hyperplasia and spongiosis



GASTROESOPHAGEAL REFLUX DISEASE (GERD)

MORPHOLOGY

- Endoscopy: Variable findings from normal to erythema/hyperemia to erosion/ulceration depending upon the severity
- Characteristic but non-specific pattern of injury includes intercellular edema/**spongiosis**, **basal cell hyperplasia,** elongation of the vascular papilla, mucosal capillary ectasia, **scattered intraepithelial inflammatory cells** (including eosinophils, lymphocytes, and neutrophils)
- Usually more prominent in the distal aspect near the GEJ



Pseudohyphae and yeast forms, GMS stain (top left)

CANDIDA ESOPHAGITIS

MORPHOLOGY

- Endoscopy: **White plaques**, usually easily scraped off to reveal erythematous or ulcerated underlying mucosa
- **Fungal pseudohyphae and budding yeast** forms with squamous debris or active esophagitis or necrosis/ulceration
- Stains with GMS and PAS histochemical stains

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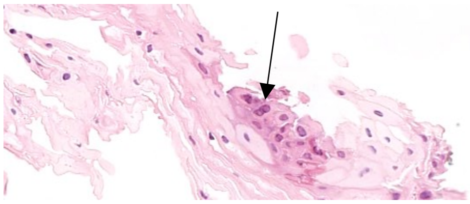
Herpes Simplex esophagitis (viral cytopathic effect)



HERPES SIMPLEX VIRUS ESOPHAGITIS

MORPHOLOGY

- Endoscopy: **Shallow ulcers** and vesicles
- Ulcer with necrotic exudate and viral cytopathic effects in the epithelial cells featuring ground glass nuclei due to **margination of chromatin, multinucleation**, and **nuclear molding (3Ms)**

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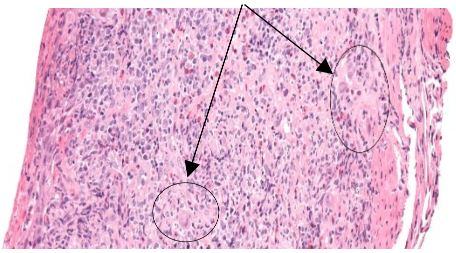
5. GASTROINTESTINAL PATHOLOGY

CMV esophagitis (viral inclusions)



CYTOMEGALOVIRUS ESOPHAGITIS

MORPHOLOGY

- Endoscopy: Erythema, erosions, or **ulceration**
- Ulcer with active esophagitis and viral cytopathic effects in the mesenchymal cells featuring enlarged cells with nucleomegaly and inclusions
- Characteristic **owl's-eye intranuclear inclusions** and **granular intracytoplasmic inclusions**

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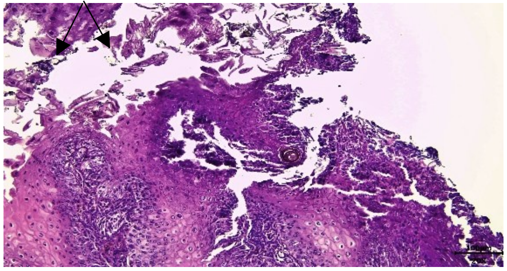
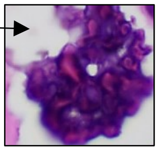
Polarizable foreign material (microcrystalline cellulose)



PILL/MEDICATION-INDUCED ESOPHAGITIS

MORPHOLOGY

- Endoscopy: Ulceration
- Ulceration, inflammatory exudate (neutrophils), and polarizable foreign material/ pill-filler material (refractile, transparent **microcrystalline cellulose** and/or purple-pink **crospovidone**)



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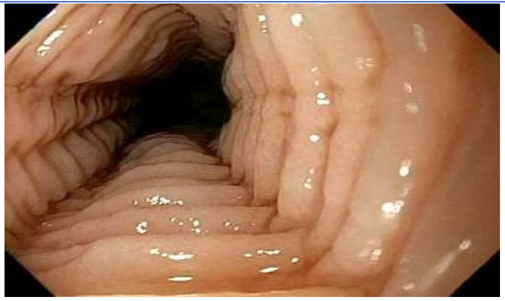
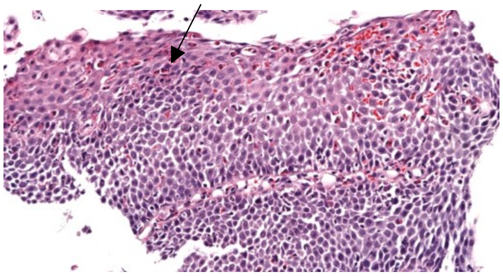


Esophageal 'trachealization"

Intraepithelial eosinophils



EOSINOPHILIC ESOPHAGITIS

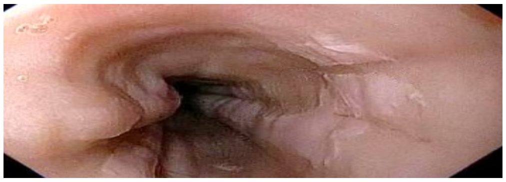
MORPHOLOGY

- Endoscopy: **Concentric rings** or linear furrows (trachealization/felinization), and white plaques or exudates
- Increased intraepithelial **eosinophils (≥15 per HPF**), eosinophilic microabscesses, superficial concentration of eosinophils with degranulation, and surface desquamation
- Other minor histologic features include basal cell hyperplasia, intercellular edema/spongiosis, elongated papillae, and lamina propria fibrosis

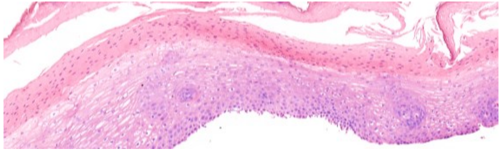
OTHER HIGH YIELD POINTS

- Immune/antigen-driven type 2 helper (Th2) T-cell mediated chronic disorder of children and adults
- **Clinicopathologic diagnosis** based on clinical features (dysphagia, food impaction, and feeding intolerance), endoscopic appearance, ≥15 intraepithelial eosinophils per HPF, and exclusion of other causes of eosinophilia
- Associated with "Atopic Triad" (**Allergies, Asthma, Eczema**)
- Often diffuse involvement of the esophagus/worse proximally

Path Presenter



Two-tone appearance with epithelial splitting



ESOPHAGITIS DISSECANS SUPERFICIALIS (SLOUGHING ESOPHAGITIS)

MORPHOLOGY

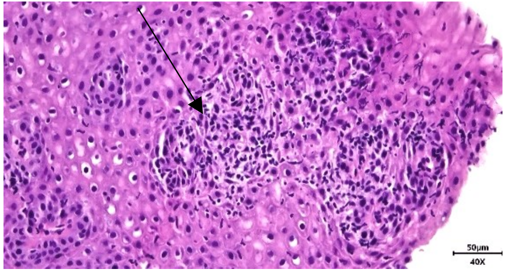
- Endoscopy: White plaques of peeling and **sloughing epithelium**
- Characteristic two-tone appearance, **superficial hypereosinophilic/necrotic epithelium with parakeratosis** and underlying viable uninflamed/minimally inflamed deeper layers; reactive basal zone hyperplasia
- Edema and vacuolization of this interface will eventually → **splitting** of squamous epithelium

Path Presenter

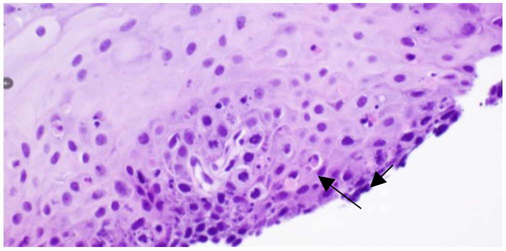
OTHER HIGH YIELD POINTS

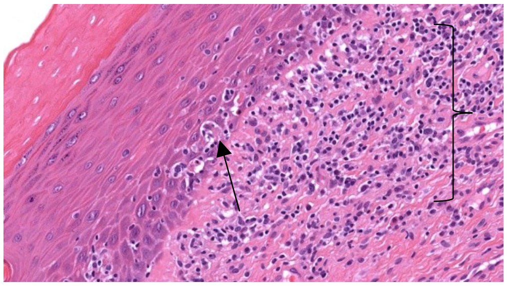
- Variable associations including multiple medications, autoimmune bullous dermatoses, thermal and chemical injury, heavy smoking, alcohol, and patients with multiple comorbidities

Intraepithelial lymphocytosis



GVHD: Scattered apoptotic bodies in esophageal mucosa





Civatte body (arrow) Band-like infiltrate

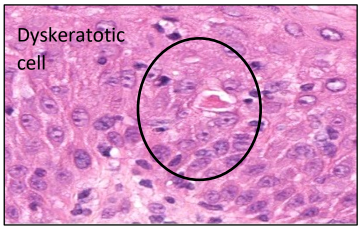
LYMPHOCYTIC ESOPHAGITIS

MORPHOLOGY

- Endoscopy: May mimic eosinophilic esophagitis including rings, furrows, and while plaques
- **Increased intraepithelial lymphocytes** concentrated around dermal papillae
- Associated **intercellular edema/spongiosis** and **dyskeratotic epithelial cells**

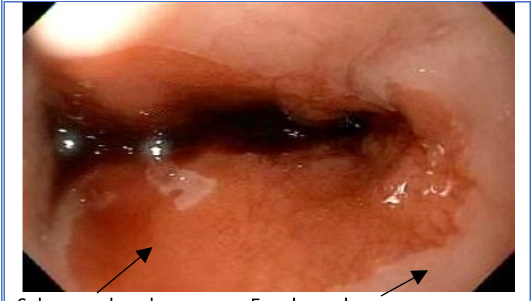
OTHER HIGH YIELD POINTS

- This pattern of injury is seen in **GERD, Crohn disease, Celiac disease, achalasia and other types of dysmotilities, lichen planus, common variable immunodeficiency, and graft-versus-host disease (GVHD)**
- **Lichen planus:**
  - Intraepithelial lymphocytosis
  - Band-like (lichenoid) lymphocytic infiltrate at interface between epithelium and lamina propria
  - Dyskeratotic keratinocytes (Civatte bodies)
  - Associated with cutaneous lichen planus, medications, viral infections, and rheumatologic disorders
  - Risk of dysplasia and progression to squamous cell carcinoma has been described
- **GVHD:**
  - Intraepithelial lymphocytosis with dyskeratotic keratinocytes and scattered apoptotic bodies
  - Typically presents with rash, diarrhea, and/or elevated liver enzymes

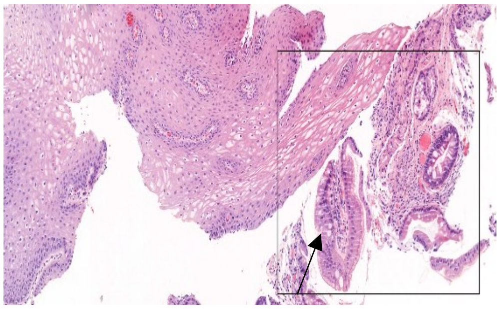


Path Presenter

BARRETT'S ESOPHAGUS, PRECURSOR LESIONS AND CARCINOMAS



Salmon-colored mucosa Esophageal squamous mucosa



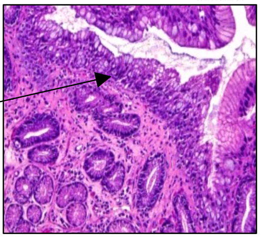
Goblet cells in gastroesophageal mucosa

BARRETT'S ESOPHAGUS (BE)

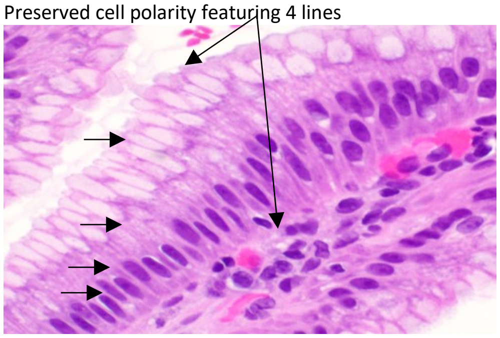
- **Extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the GEJ on endoscopy, with biopsy confirmation of intestinal metaplasia (defined by presence of goblet cells)**
- Risk factors: Chronic GERD, male gender, Caucasians, central obesity, smoking, and age >50 years
- Pathogenesis: Chronic GERD induced tissue damage→ **Upregulation of columnar transcription factors (SOX9)**, induces columnar differentiation→ Upregulation of intestinal differentiation factors (CDX2) → Intestinal metaplasia→ Molecular alterations→ Low-grade dysplasia→ Additional mutations like *TP53* and DNA aneuploidy→ High-grade dysplasia and carcinoma

Path Presenter

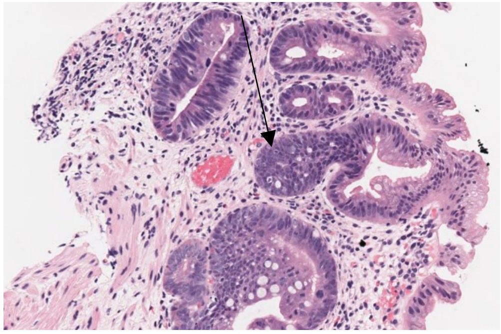
- **Alcian-blue/PAS stain**: highlights goblet cells (blue color)
- True goblet cells: rounded/ovoid shape, clear to slightly blue-tinged cytoplasmic mucin, eccentrically located nucleus and typically randomly distributed
- **Multilayered epithelium**: Immature squamoid cells in the basal layer and superficial acid mucin containing non-goblet columnar cells; considered a marker of GERD and potential precursor to Barrett's esophagus



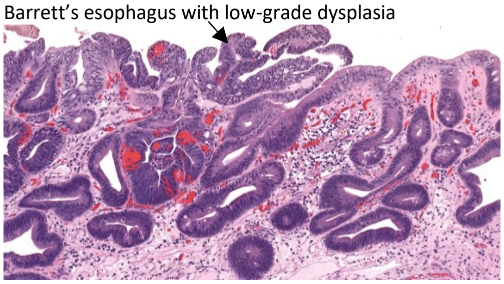
Preserved cell polarity featuring 4 lines



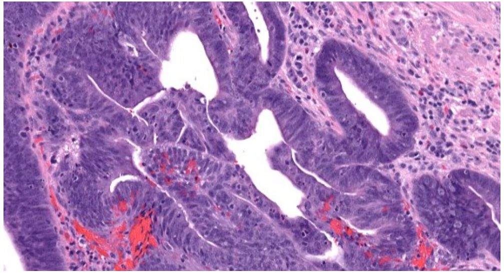
Barrett's esophagus with basal crypt dysplasia



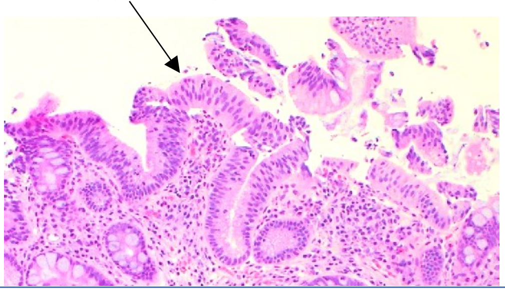
Barrett's esophagus with low-grade dysplasia



High-grade dysplasia



Foveolar dysplasia (low grade)



DYSPLASIA IN BARRETT'S ESOPHAGUS

MORPHOLOGY

Negative for dysplasia:

- Surface maturation and preserved cell polarity showing the four lines (best seen in well-aligned tissue)
  - Apical neutral mucin cap
  - Base of the mucin cap
  - Eosinophilic cytoplasm below the mucin
  - Row of nuclei
- Endoscopic surveillance interval of every 3-5 years

Indefinite for dysplasia:

- Used when it is uncertain whether the changes (nuclear enlargement and hyperchromasia) seen are reactive/reparative versus neoplastic
- Significant inflammation or ulceration are obscuring the findings
- Technical artifacts and thermal effect on tissues limit the interpretation
- Treat for GERD and repeat biopsy in 3-6 months

Low-grade dysplasia: Adenoma-like or intestinal type

- Cytological abnormality with little or no architectural complexity
- Nuclear enlargement, hyperchromasia, and stratification with retained nuclear polarity
- The findings extend to surface epithelium and often show abrupt transition from non-dysplastic to dysplastic area
- Managed by endoscopic mucosal ablation

High-grade dysplasia:

- Greater degree of cytological atypia often along with architectural abnormality; no surface maturation
- Marked nuclear enlargement, pleomorphism, irregular nuclear contours, loss of polarity, and hyperchromasia
- Crowded crypts with variable size and shape, cribriforming, and back-to-back arrangement

Foveolar (non-intestinal) dysplasia:

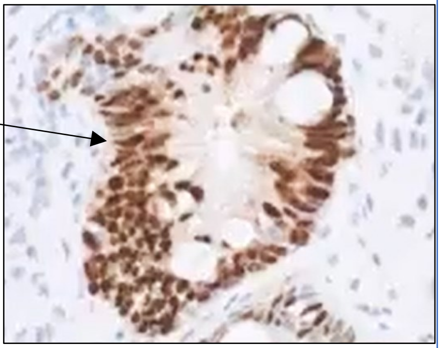
- Few, if any, goblet cells
- Typically composed of a single layer of foveolar type columnar cells with prominent cytoplasmic mucin
- Hyperchromatic slightly enlarged nuclei without stratification
- High-grade foveolar dysplasia shows markedly increased nuclear size and open chromatin, prominent nucleoli, and increased mitoses

Basal crypt dysplasia:

- Marked cytological atypia at the base of the crypt that matures at the surface

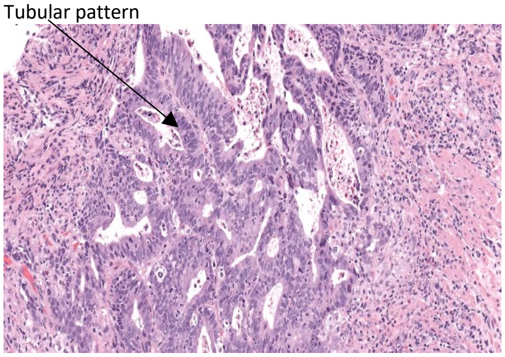
OTHER HIGH YIELD POINTS

- **Aberrant p53 immunohistochemical stain** expression is considered significant for dysplasia
  - Overexpression: Strong and diffuse positivity in every nucleus
  - Null phenotype: Absent staining

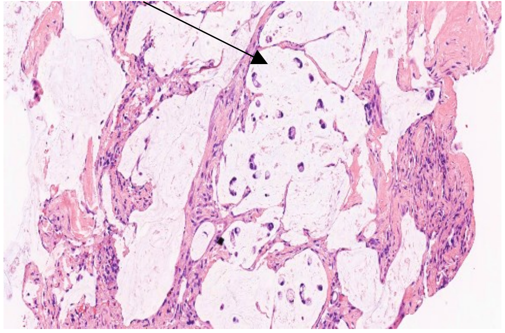


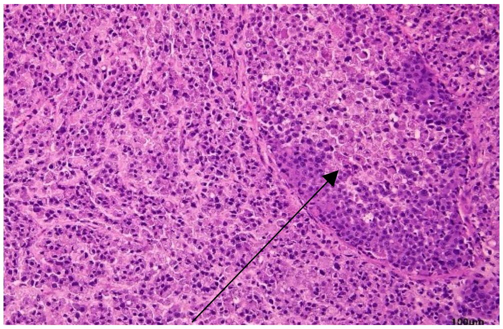
Path Presenter Path Presenter

Tubular pattern

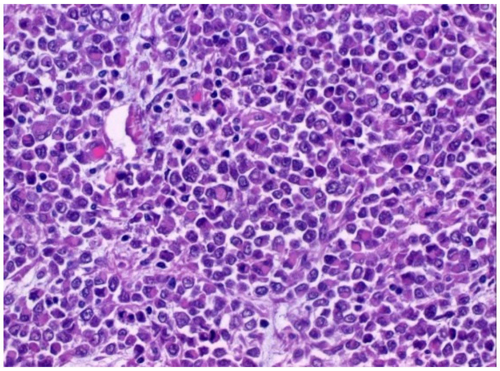


Mucinous pattern





Signet-ring cell pattern



Undifferentiated carcinoma with rhabdoid morphology

ADENOCARCINOMA

MORPHOLOGY

- Gross: Polypoid, fungating, ulcerated or diffuse infiltrative lesions
- Microscopy: Shows gastric, intestinal and mixed lineage with tubular, papillary, mucinous or signet-ring cell growth pattern
- **Tubular pattern**: Most common, characterized by irregular single or anastomosing glandular structures
- **Papillary pattern**: Form papillae, rare cases show micropapillary pattern
- **Mucinous pattern**: Tumor cells float in abundant extracellular mucin
- **Signet-ring cell pattern**: Worse prognosis

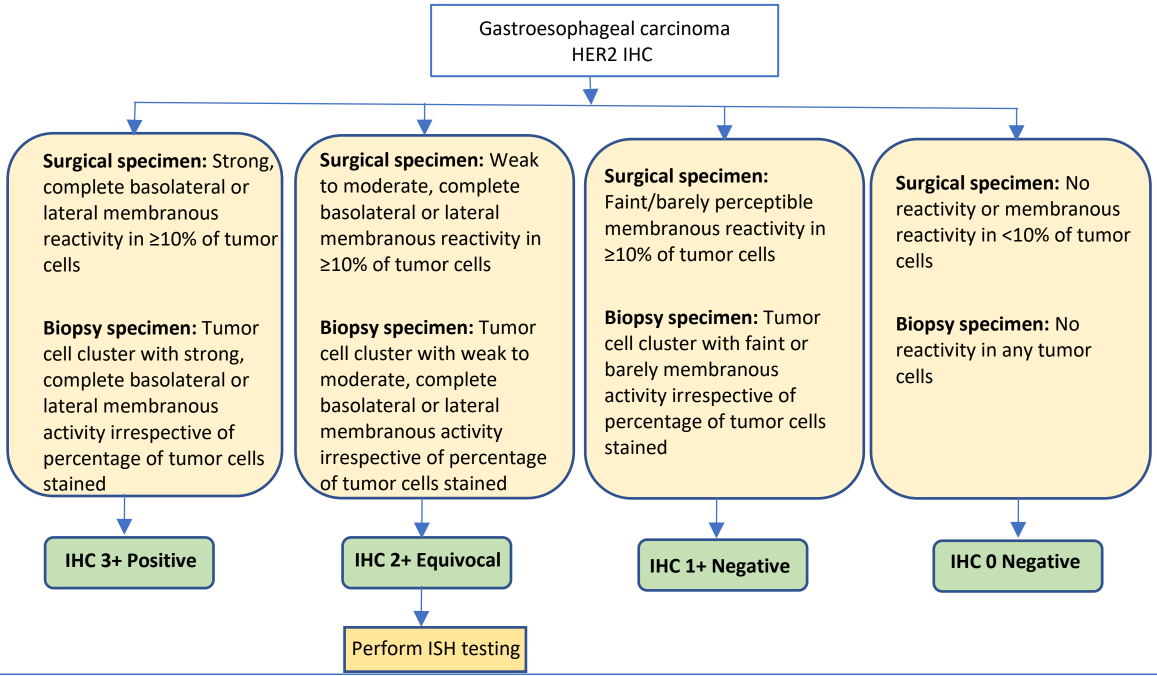
OTHER HIGH YIELD POINTS

- Presence of invasive features such as tumor budding (defined as the presence of detached, isolated groups of 1–5 cells) and irregular angulated glands into lamina propria and muscularis mucosae are defined as pT1a or intramucosal carcinomas
- Glandular luminal necrosis, prominent nucleoli, and glands growing parallel to the surface are other features of early intramucosal carcinoma
- Hints that deep invasion is present on mucosal biopsies: Prominent desmoplasia and/or pagetoid extension of carcinoma cells in the squamous epithelium
- Endoscopic resection with or without radiofrequency ablation is the standard of treatment for pT1 esophageal adenocarcinomas that do not show adverse pathological features
- **Adverse pathological features include submucosal invasion (pT1b) to a depth > 500 µm, poor differentiation, lymphovascular invasion, and positive margins**
- **Muscularis mucosae is commonly duplicated** and thickened in the setting of Barrett's esophagus and invasion of this layer should not be misinterpreted as invasion of muscularis propria
- Advanced carcinomas require esophagectomy, possibly after chemoradiation
- **HER2 testing** is done routinely and if amplified is approved for treatment with Trastuzumab
- The immunotherapy agent pembrolizumab has shown promising early results for the treatment of advanced and metastatic esophagogastric junction adenocarcinomas
- It can be difficult to distinguish a poorly differentiated adenocarcinoma from a poorly differentiated squamous cell carcinoma (SCC), particularly in biopsy specimens
- Undifferentiated carcinoma should be considered if the immunohistochemical pattern is equivocal or if there are no definite morphologic features

IHC panel for Adenocarcinoma versus SCC

Adenocarcinoma	Squamous cell carcinoma
CK7+	CK7- (usually)
CK5/6, p63, and p40-	CK5/6, p63, and p40+
PAS and mucin+	PAS and mucin-

Path Presenter



Gastroesophageal carcinoma
HER2 IHC

Surgical specimen: Strong, complete basolateral or lateral membranous reactivity in ≥10% of tumor cells

Biopsy specimen: Tumor cell cluster with strong, complete basolateral or lateral membranous activity irrespective of percentage of tumor cells stained

IHC 3+ Positive

Surgical specimen: Weak to moderate, complete basolateral or lateral membranous reactivity in ≥10% of tumor cells

Biopsy specimen: Tumor cell cluster with weak to moderate, complete basolateral or lateral membranous activity irrespective of percentage of tumor cells stained

IHC 2+ Equivocal

Perform ISH testing

Surgical specimen: Faint/barely perceptible membranous reactivity in ≥10% of tumor cells

Biopsy specimen: Tumor cell cluster with faint or barely membranous activity irrespective of percentage of tumor cells stained

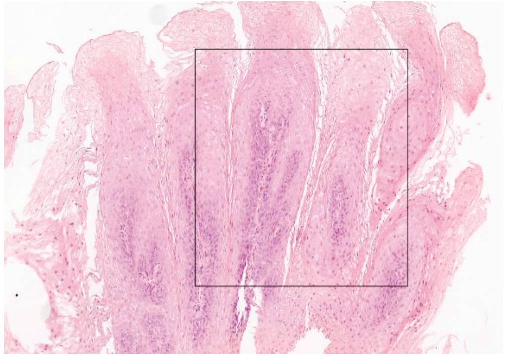
IHC 1+ Negative

Surgical specimen: No reactivity or membranous reactivity in <10% of tumor cells

Biopsy specimen: No reactivity in any tumor cells

IHC 0 Negative

Papillary proliferation with fibrovascular cores



SQUAMOUS PAPILLOMA

Path Presenter

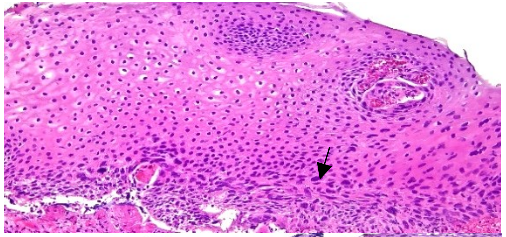
MORPHOLOGY

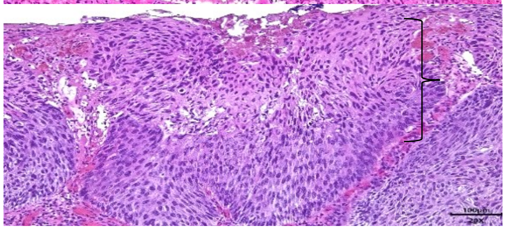
- Gross: Usually small **polypoid lesions** with a warty surface
- **Benign papillary proliferation of the squamous epithelium with fibrovascular core of lamina propria**
- Vacuolated cells with morphological features of **koilocytes** can be seen without atypical nuclear features
- Usually exophytic, but can be flat/endophytic

OTHER HIGH YIELD POINTS

- Result from mucosal irritation, caused by GERD, trauma, or HPV infection, stimulating a hyper-regenerative response
- Typically, in distal esophagus in the US population, but in Asian population more frequently seen in the mid esophagus

Low grade dysplasia





High grade dysplasia

SQUAMOUS DYSPLASIA

Path Presenter

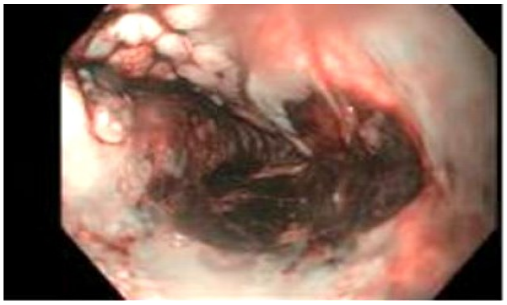
MORPHOLOGY

- Gross: Flat lesions are better **highlighted by Lugol iodine solution**
- Diagnosis requires both cytologic and architectural atypia
  - Cytologic atypia: Nuclear enlargement, pleomorphism, hyperchromasia, loss of polarity, and nuclear overlap
  - Architectural Atypia: Abnormal epithelial maturation
- **Low-grade and High-grade dysplasia (two-tier)** are the WHO recommended grading system
- **Low-grade dysplasia:** Involvement of the **lower half of the epithelium** only with mild atypia
- **High-grade dysplasia:** Involvement of **more than half of the epithelium or severe cytologic atypia** is present regardless of the extent of the epithelial involvement

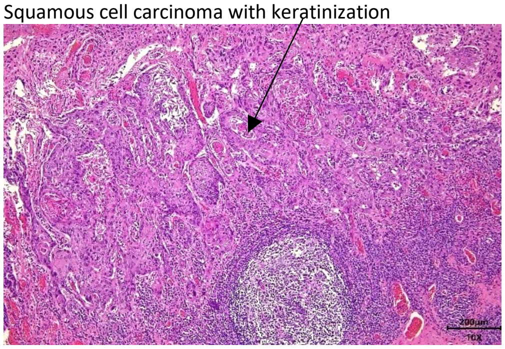
OTHER HIGH YIELD POINTS

- Risk factors are similar to those of esophageal squamous cell carcinoma

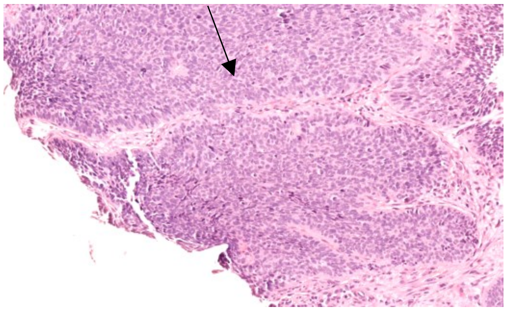
Ulcerated lesion



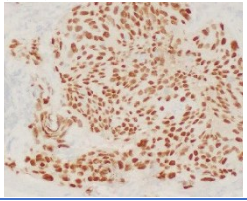
Squamous cell carcinoma with keratinization



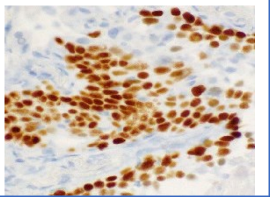
Basaloid squamous cell carcinoma



p40 positive



p63 positi



SQUAMOUS CELL CARCINOMA (SCC)

Path Presenter

MORPHOLOGY

- Gross: Exophytic or ulcerated mass lesion
- Malignant epithelial neoplasm showing squamous differentiation characterized by keratinocyte-type cells with intercellular bridges and/or keratinization
- Grading is based on the degree of cytological atypia, mitotic activity, and presence of keratinization

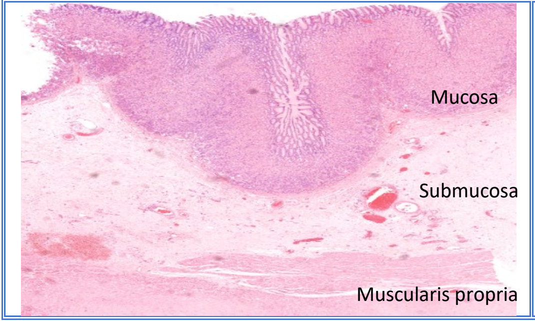
SUBTYPES:

- **Verrucous SCC:** Exceedingly well-differentiated squamous cells with minimal cytological atypia, minimal mitotic activity, surface papillary projections, and invasive front characterized by broad bulbous pushing projections
  - ➢ Often arises in the setting of chronic irritation, esophagitis, or previous injury
- **Spindle cell SCC:** Polypoid growth pattern with biphasic pattern of neoplastic squamous epithelium and spindle cells
  - ➢ Squamous elements are usually well to moderately differentiated or may be carcinoma in situ alone
  - ➢ The spindle cell component is a high-grade malignancy, which may show osseous, cartilaginous, or skeletal muscle differentiation
- **Basaloid SCC:** Solid or nested growth pattern of basaloid cells, sometimes with central comedo necrosis and occasionally with pseudoglandular/cribriform formations
  - ➢ Unlike basaloid SCC in the oropharynx, **esophageal one has no association with HPV infection**

OTHER HIGH YIELD POINTS

- Risk factors: Tobacco, alcohol, drinking hot beverages, dietary and genetic factors, medical conditions like Plummer-Vinson syndrome, achalasia, and radiotherapy, caustic ingestion, and HPV infection
- In most cases, HPV appears to be an innocent bystander; viral integration and transcription is uncommon, and the current consensus is that HPV infection is unlikely to be a substantial risk factor
- Accumulating genetic abnormalities drive progression from normal→ low-grade dysplasia→high-grade dysplasia→invasive carcinoma
- ***TP53* mutation** is a key early driver mutation
- **Tylosis**, an autosomal dominant keratosis disorder caused by a missense mutation in *RHBDF2*, is associated with familial early onset esophageal SCC
  - ➢ Epidermoid metaplasia/Esophageal leukoplakia: Characterized by prominent granular layer with keratohyalin granules, like in epidermis of skin, along with surface orthokeratosis

STOMACH

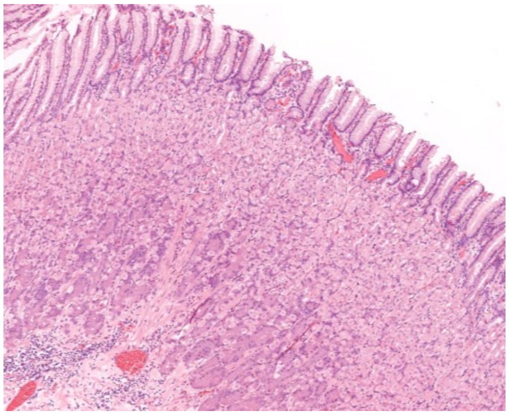


NORMAL

HISTOLOGY

- **Mucosa:** Comprised of lining epithelium, lamina propria, and muscularis mucosa
- Gastric pits and deep glands are the two compartments of mucosa
  - ➢ Gastric pits or surface invaginations: Lined by neutral mucin containing foveolar cells throughout the stomach
  - ➢ Deep glands: Vary with anatomic regions
  - ➢ Cardiac and antrum/pylorus: Comprised of mucus secreting glands
  - ➢ Fundus and body (Oxyntic mucosa): Comprised of pink parietal cells that

Gastric oxyntic/body mucosa

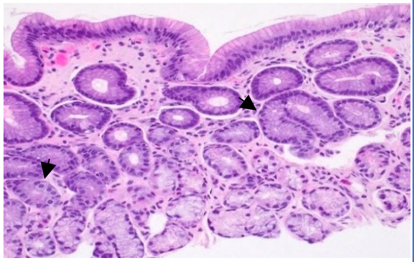


Pink=parietal cells, blue-chief cells

produce acid and intrinsic factor (for B12 absorption) and purple chief cell that produce pepsinogen

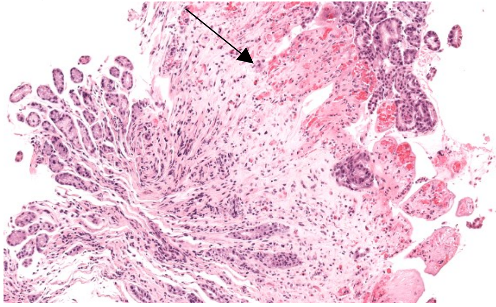
- Endocrine cells are present throughout mucosa, but gastrin-secreting **G-cells** are normally found only in the antrum
- **Submucosa:** Loose connective tissue containing blood vessels, lymphatics, nerve fibers, and ganglion cells
- **Muscularis propria:** Inner oblique, middle circular and outer longitudinal layer of smooth muscles, and myenteric plexus
- **Subserosa and serosa:** Thin layer of collagen and lining mesothelium

Arrows mark the G-cells



INFLAMMATORY/NON-NEOPLASTIC CONDITIONS

Congested mucosal capillaries with hemorrhage



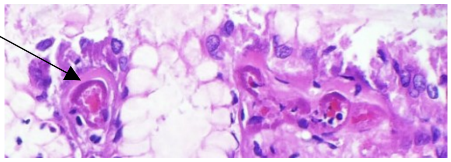
Path Presenter

ACUTE HEMORRHAGIC GASTRITIS

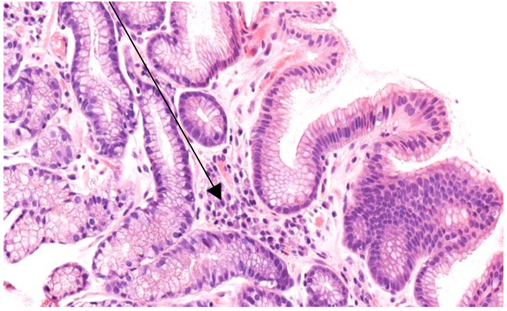
- Characterized by hyperemic edematous mucosa with bleeding, erosions, and ulcers
- Microscopy: **Dilatation and congestion of mucosal capillaries, edema, lamina propria hemorrhage**, and superficial erosions with fibrin and neutrophils
- Usual etiologic factors include severe stress, trauma, shock, binge drinking, caustic agents, large doses of NSAIDs, steroids, and doxycycline

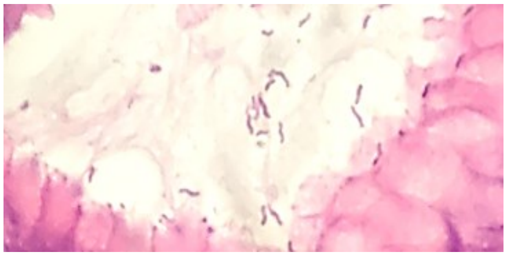
OTHER HIGH YIELD POINTS

- **Fibrinoid necrosis of superficial capillaries can be seen in the setting of doxycycline gastritis**
- Adjacent epithelium may show reactive changes with mucin depletion



Superficial mononuclear inflammatory infiltrate





H.pylori immunohistochemical stain

HELICOBACTER PYLORI GASTRITIS (H. Pylori gastritis)

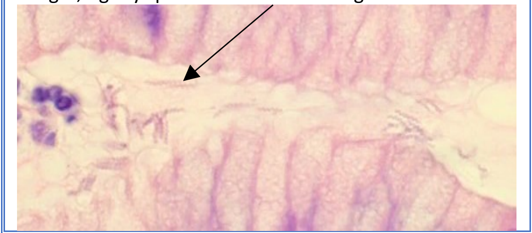
MORPHOLOGY

- Most common treatable form of chronic gastritis caused by gram negative curved rods
- Endoscopy: Varies from erythema, erosions, hypertrophy or atrophic changes
- **Superficial mononuclear (lymphoplasmacytic) inflammatory infiltrate** with prominent lymphoid follicles and musical neutrophils
- Slender curved bacilli are typically seen in the mucin coat of lining epithelial cells and intracellular invasion has been seen in patients received proton pump inhibitor therapy (PPI); coccoid forms can also be seen after PPI treatment
- After successful eradication therapy, acute inflammation disappears rapidly, however chronic inactive inflammation persists longer

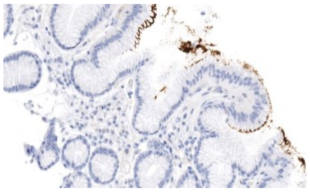
OTHER HIGH YIELD POINTS

- Commonly colonize the antrum first but can eventually progress to pangastritis→ mucosal atrophy→ intestinal metaplasia→ dysplasia→ carcinoma
- Major **risk factor for development of extranodal marginal zone lymphoma** of mucosa-associated lymphoid tissue

Longer, tightly spiraled H.heilmannii organisms

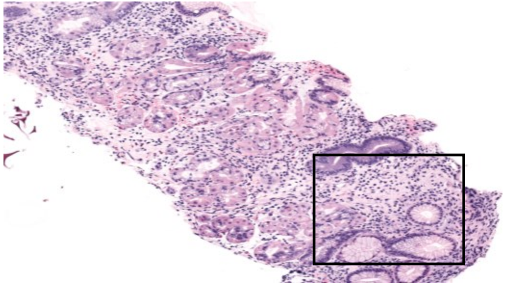


- *Helicobacter heilmannii* gastritis: Infection acquired from farm animals and household pets, therefore more common in children, histologic findings are similar to H.pylori gastritis but usually less severe
    - **Longer, more tightly spiraled bacilli** seen in the lumen

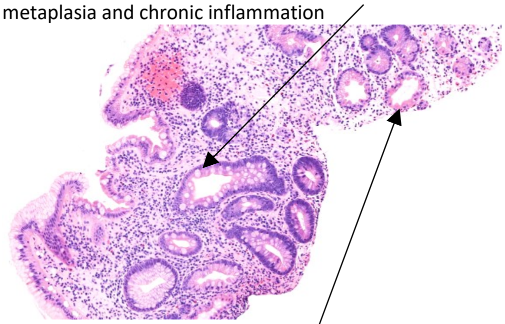


Path Presenter

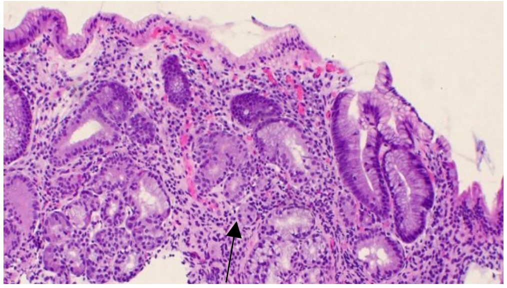
Early phase: Dense lamina propria inflammation and patchy loss of oxyntic cells (see box)



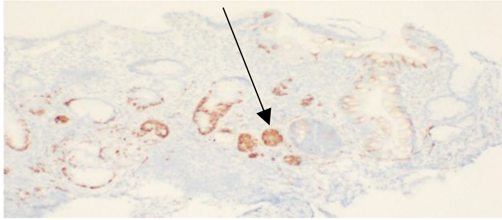
Florid phase: Atrophic oxyntic mucosa with intestinal metaplasia and chronic inflammation



Residual parietal cells



Neuroendocrine cell hyperplasia (Synaptophysin)



AUTOIMMUNE GASTRITIS

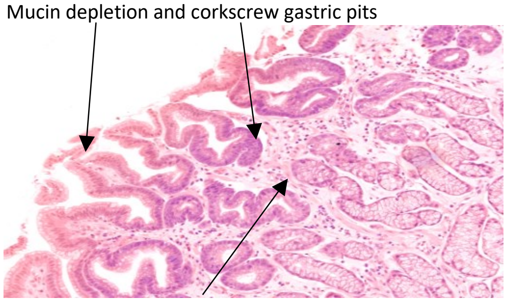
MORPHOLOGY

- Gastric **oxyntic mucosa-restricted** chronic atrophic gastritis
- Associated with circulating **anti-parietal cell** and **anti-intrinsic factor antibodies**
- Antrum may be normal or features reactive gastropathy changes and G- cell hyperplasia
- Endoscopy: Atrophic body mucosa with absence of rugal folds and in advanced disease hyperplastic polyp formation
- Early, florid and end stage are the three pathologic phases identified in the course of disease
- **Early phase**:
    - Diffuse or multifocal, dense lamina propria lymphoplasmacytic infiltration often mixed with eosinophils and mast cells
    - Patchy lymphocytic infiltration with destruction of individual oxyntic gland may be seen
    - Patchy pseudo-pyloric metaplasia and hypertrophic changes of the residual parietal cells
    - Intestinal metaplasia is rare
- **Florid phase**:
    - Marked atrophy of oxyntic glands and lamina propria diffuse lymphoplasmacytic infiltration
    - Extensive pseudopyloric metaplasia
    - Prominent intestinal metaplasia
- **End stage**:
    - Marked reduction in oxyntic glands, foveolar hyperplasia and hyperplastic polyp formation
    - Increasing degrees of pseudopyloric, pancreatic, and intestinal metaplasia
    - Parietal cells are hard to detect, and inflammation is reduced
    - Linear or nodular enterochromaffin-like (ECL) cell hyperplasia secondary to achlorhydria→ physiologic hypergastrinemia
- Can **progress to intramucosal and invasive neuroendocrine tumors**

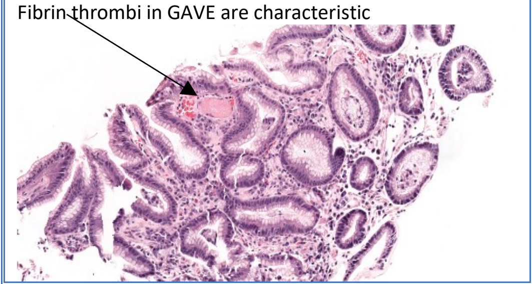
OTHER HIGH YIELD POINTS

- Lack of intrinsic factor→ B12 deficiency→ Pernicious anemia
- Gastrin stain can help confirm sample came from gastric body (negative) and not antrum (positive)
- Synaptophysin and chromogranin stain highlight ECL hyperplasia

Path Presenter


Mucin depletion and corkscrew gastric pits

Smooth muscle bands in the lamina propria


Fibrin thrombi in GAVE are characteristic

REACTIVE (CHEMICAL) GASTROPATHY

MORPHOLOGY

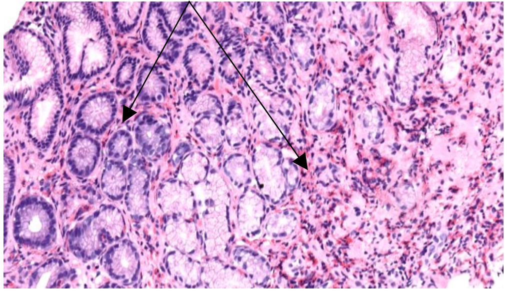
- Endoscopy: Mucosal erythema and edema
- **Foveolar hyperplasia (tortuous/corkscrew gastric pits)**
- **Mucin depletion**, edema, and ectatic capillaries
- **Extension of smooth muscle bands in the lamina propria** and minimal inflammation

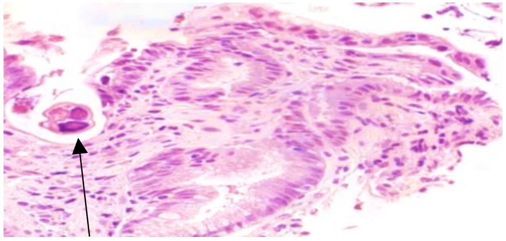
OTHER HIGH YIELD POINTS

- Often caused by chemical irritation by bile reflux, chronic use of medications like NSAIDs and iron, alcohol or chemoradiation therapy
- **Gastric antral vascular ectasia (GAVE)**: Endoscopic appearance of **watermelon stomach** due to hyperemic mucosal streaks converging on antrum; Overall resembles reactive gastropathy with antral vascular ectasia and **intravascular fibrin thrombi**
- **Portal hypertensive gastropathy**: Occurs in cirrhotic or non-cirrhotic portal hypertension, endoscopically **mosaic or snake-skin pattern** of edematous mucosa, histology like reactive gastropathy with dilated capillaries and veins in mucosa and submucosa

Path Presenter

Increased eosinophils in gastric mucosa




Strongyloides in gastric mucosal biopsy

EOSINOPHILIC GASTRITIS/GASTROENTERITIS

MORPHOLOGY

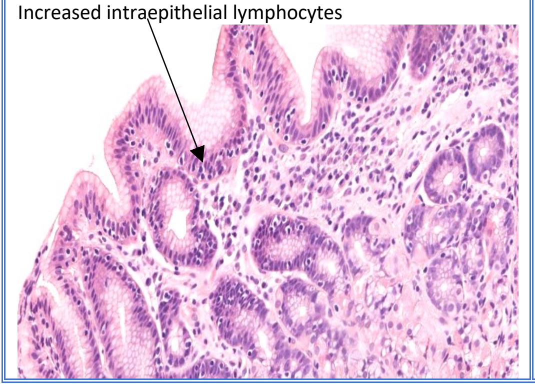
- Increased eosinophilic infiltration of the gastrointestinal tract (stomach, small intestine, or colon)
- Although there is no established cut-off to diagnose the entity, **>30 eosinophils/HPF in five HPFs** is likely too many
- **Presence of intraepithelial eosinophils with eosinophilic crypt abscesses, eosinophils in muscularis mucosae and submucosa are abnormal**
- Other associated findings may see include edema, erosion, reactive epithelial changes, and mast cell infiltration

OTHER HIGH YIELD POINTS

- Etiology is unknown for primary eosinophilic gastrointestinal disorder and is a diagnosis of exclusion
- Secondary gastric tissue eosinophilia is seen in food allergies, H. pylori, parasitic (*Strongyloides* and *Anisakis* spp.) infections, medications, inflammatory bowel disease, and connective tissue diseases/vasculitis

Path Presenter

Increased intraepithelial lymphocytes



LYMPHOCYTIC GASTRITIS

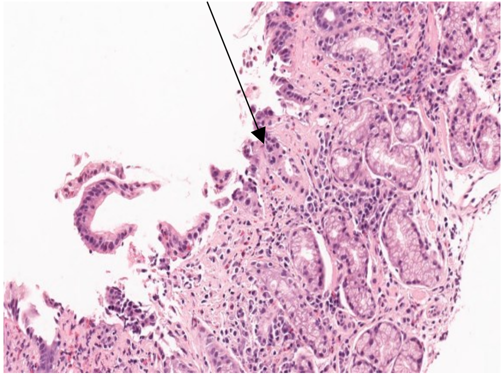
Path Presenter

- Chronic gastritis characterized by increased numbers of mature **intraepithelial (surface and foveolar) lymphocytes**
- Endoscopy: Varies from normal to mucosal nodularity with erosions (varioliform gastritis)
- **Increased intraepithelial lymphocytes (> 25 per 100 epithelial cells),** along with mixed lymphoplasmacytic infiltration of lamina propria
- Lack of lymphoepithelial lesions

OTHER HIGH YIELD POINTS

- Associated with celiac disease, H. pylori infection, HIV, medications (Ticlopidine, Immune-check point inhibitors, NSAIDs), Crohn disease, Ménétrier disease, and lymphocytic and collagenous colitis

Thickened subepithelial collagen layer



COLLAGENOUS GASTRITIS

MORPHOLOGY

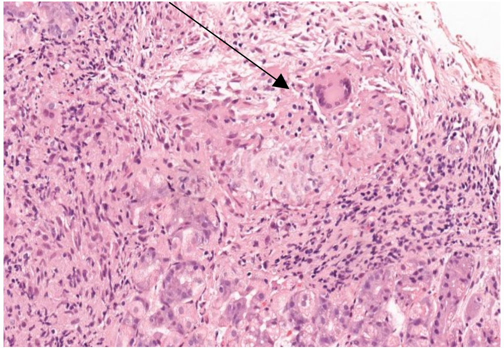
- **Diffuse or patchy thickened subepithelial collagen band (trichrome+)**, having a thickness of **> 10 µm, often with entrapped inflammatory cells and capillaries** in the collagen band; other findings include increased intraepithelial lymphocytosis and lamina propria lymphoplasmacytic infiltration with intermixed eosinophils

OTHER HIGH YIELD POINTS

- Pediatric patients and young adults usually present with anemia, upper GI symptoms, and disease related to gastric mucosa
- Adults may present with associated collagenous/lymphocytic colitis, celiac disease, and lymphocytic gastritis

Path Presenter

Gastric mucosal granuloma



GRANULOMATOUS GASTRITIS

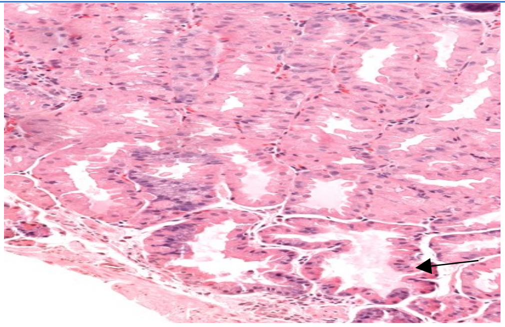
MORPHOLOGY

- Histologic pattern of disease entity characterized by multiple gastric mucosal granulomas
- Number, location, and type of granuloma are variable depending upon the etiology

OTHER HIGH YIELD POINTS

- Usual etiologies include **infections (tuberculosis, fungal, parasitic), systemic conditions (sarcoidosis, Crohn's disease, common variable immunodeficiency, rarely Langerhan cell histiocytosis), foreign bodies, and lymphoma**

Path Presenter



PROTON PUMP INHIBITOR THERAPY EFFECT

MORPHOLOGY

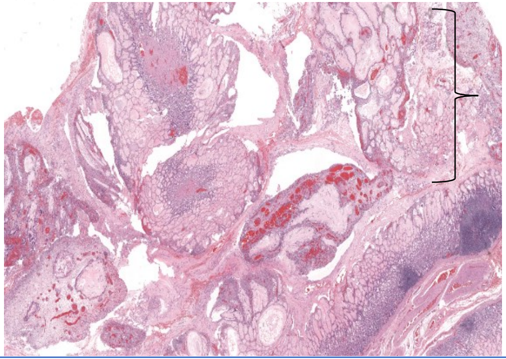
- **Dilated oxyntic glands** with hypertrophic parietal cells having snouts or cytoplasmic blebs

OTHER HIGH YIELD POINTS

- Associated with any type of proton pump inhibitor use
- Increases gastrin levels through feedback, causing parietal cell hypertrophy
- Long term therapy may lead to fundic gland polyps

Path Presenter

Thickened folds characterized by marked foveolar hyperplasia



MÉNÉTRIER DISEASE

MORPHOLOGY

- Hyperplastic gastropathy characterized by thickened body/fundus folds, low acid production, and **protein losing enteropathy**
- **Marked foveolar hyperplasia** with tortuous gastric pits and cystically dilated atrophic glands
- Lamina propria with edema and variable inflammation

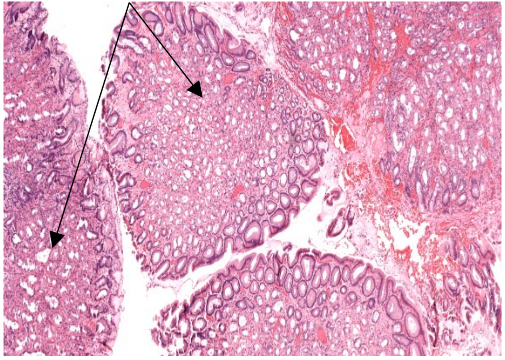
OTHER HIGH YIELD POINTS

- Pathogenetic mechanisms include increased signaling of epidermal growth factor (EGFR) and viral infections

Path Presenter

5. GASTROINTESTINAL PATHOLOGY

Foveolar hyperplasia and parietal cell hypertrophy



ZOLLINGER-ELLISON SYNDROME

Path Presenter

MORPHOLOGY

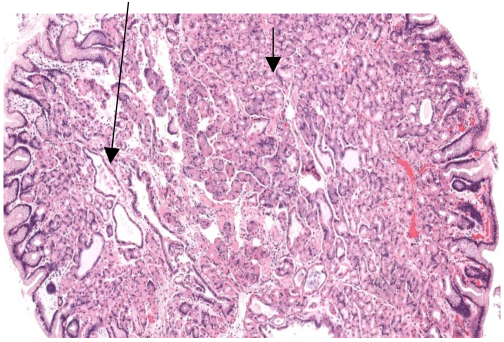
- Gastric mucosal hypertrophy and increased acid secretion caused by serum hypergastrinemia due to pancreatic or duodenal neuroendocrine tumor (gastrinoma)
- Enlarged gastric body/fundus mucosal folds and duodenal ulcers
- Foveolar hyperplasia with dilated oxyntic glands and parietal cell hypertrophy; can progress to secondary ECL-cell hyperplasia, dysplasia, and gastric neuroendocrine tumors

OTHER HIGH YIELD POINTS

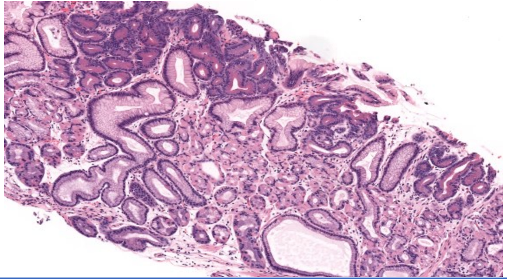
- Can develop in the setting of **multiple endocrine neoplasia (MEN)-type 1 syndrome**

BENIGN/PRECURSOR NEOPLASMS AND MALIGNANCIES

Cystically dilated oxyntic glands



Fundic gland polyp with low grade dysplasia



FUNDIC GLAND POLYPS

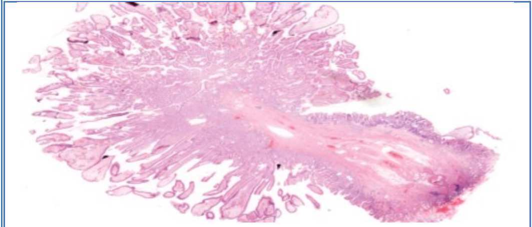
MORPHOLOGY

- Benign hyperplastic expansion of deep oxyntic mucosa with **cystically dilated oxyntic glands** and parietal cell hyperplasia
- Foveolar hyperplasia can be seen
- **Most common type of gastric polyp**, **usually sporadic, and are often associated with PPI use**
- Presence of numerous polyps in a young patient should raise the possibility of a polyposis syndrome

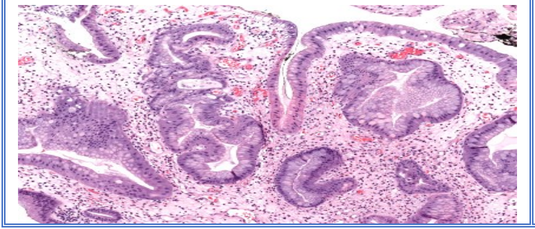
OTHER HIGH YIELD POINTS

- Associated polyposis syndromes include **familial adenomatous polyposis (FAP), Zollinger-Ellison syndrome, and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)**
- Sporadic polyps are devoid of *APC* mutations but can have mutations in ***CTNNB1*** (encoding β-catenin)
- Polyps in the setting of FAP and GAPPS harbor *APC* mutations and have increased incidence of dysplasia
- Even in FAP-associated fundic gland polyps, adenocarcinoma and high-grade dysplasia is rare
- Dysplasia in sporadic polyps is rare (<1%)

Path Presenter



Hyperplastic surface foveolar epithelium



GASTRIC HYPERPLASTIC POLYPS

Path Presenter

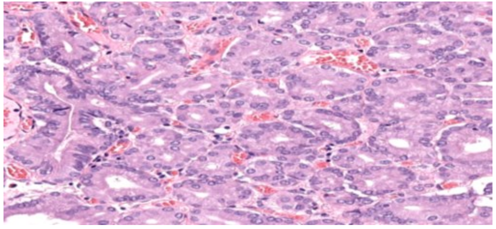
MORPHOLOGY

- Benign epithelial lesions featuring elongated, tortuous, **hyperplastic foveolar epithelium** and **cystically dilated glands** (not lined by two-cell types)
- Stromal edema, inflammation and surface erosion are often seen
- Small, haphazardly distributed smooth muscle bundles extending to the surface may be present

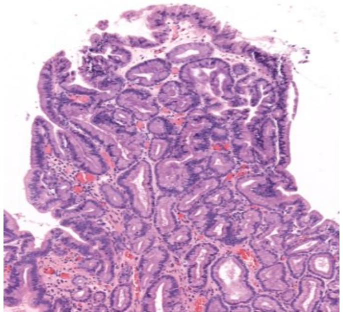
OTHER HIGH YIELD POINTS

- Second most common gastric polyp and arises as a hyperproliferative response to tissue injury
- Polypoid foveolar hyperplasia is regarded as a precursor to gastric hyperplastic polyps
- There is a strong association with **chronic gastritis, including H. pylori gastritis and post-gastrectomy gastritis**

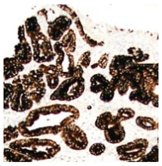
Pyloric adenoma: high power magnification

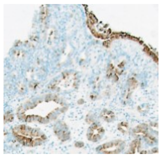


Pyloric gland adenoma:



MUC6





MUC5AC

PYLORIC GLAND ADENOMA (PGA)

MORPHOLOGY

- Polypoid proliferation of closely packed pyloric-type glands, lined by cuboidal to low-columnar epithelial cells
- Cells feature clear or lightly eosinophilic ground-glass cytoplasm with basally located nuclei and lack well-formed apical mucin cap
- PGAs can develop high-grade dysplasia and adenocarcinomas
- IHC: Diffuse MUC6 and variable MUC5AC expression

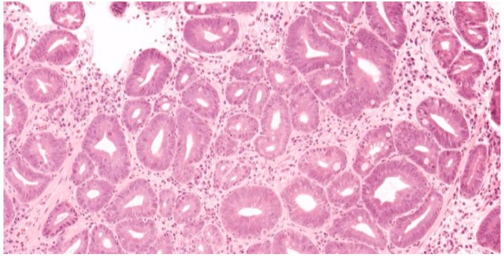
OTHER HIGH YIELD POINTS

- Sporadic cases are associated with **autoimmune atrophic gastritis**
- Can also arise in polyposis syndromes like **FAP, GAPPS, McCune–Albright syndrome, juvenile polyposis,** and **Lynch syndrome**
- Both sporadic and FAP–associated PGAs feature activating ***GNAS*** **and/or** ***KRAS*** **mutations** and **inactivating** ***APC*** **mutations**

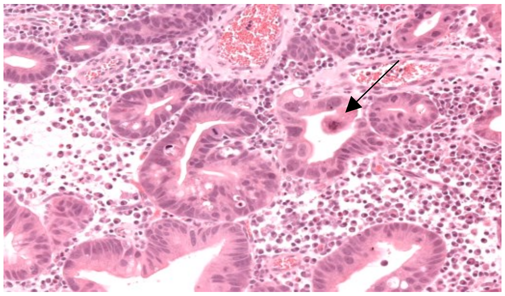
Path Presenter

IHC images courtesy of Dr. Maryam Pezhouh; used with permission

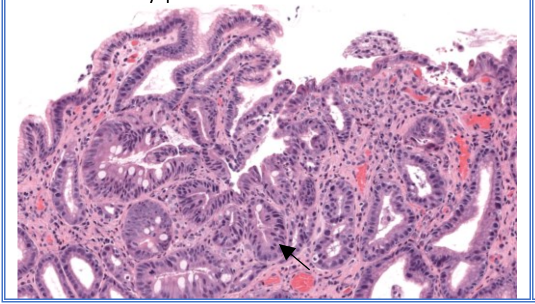
Low-grade dysplasia in the background of intestinal metaplasia



High-grade dysplasia



Indefinite for dysplasia



GASTRIC DYSPLASIA

MORPHOLOGY

- Neoplastic change of gastric epithelium without stromal invasion
- Subtypes recognized include intestinal-type, foveolar/gastric-type, gastric pit/crypt dysplasia, and serrated dysplasia
- Endoscopically appear as flat, depressed, or polypoid lesion
- Graded as low-grade or high-grade, based on degree of nuclear atypia, mitotic activity, cytoplasmic differentiation, and architectural distortion

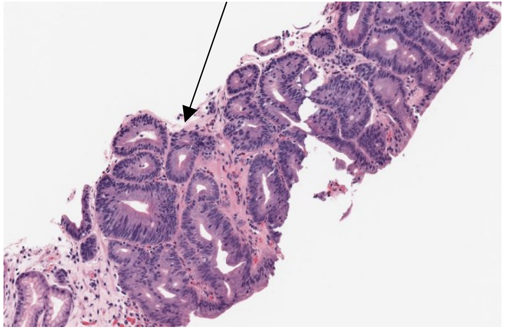
Low-grade	High-grade
Relatively preserved architecture	Complex architecture with back-to-back glands and marked distortion
Nuclei maintain polarity (basally located) **Intestinal - type: hyperchromatic, elongated (cigar-shaped) nuclei** **Foveolar - type: round to oval nuclei**	Loss of nuclear polarity (atypical nuclei extends to the luminal surface) Enlarged nuclei with a high nuclear to cytoplasmic ratio, sometimes prominent nucleoli

OTHER HIGH YIELD POINTS

- Risk factors: **H. pylori (most common),** smoking, radiation exposure, and occupation in rubber manufacturing
- Indefinite for dysplasia: Not a biologic entity; used when there are questions as to if a lesion is neoplastic or reactive
  - ➢ Often applied for biopsies with marked inflammation
- Intramucosal carcinoma: Neoplasm that invades lamina propria or muscularis mucosae and is characterized by glandular crowding, excessive branching, and budding
  - ➢ Helpful findings to look for include single-cell infiltration, trabecular growth, intraglandular necrotic debris, and irregular gland fusions

Path Presenter

Dysplastic tubules with intestinal differentiation

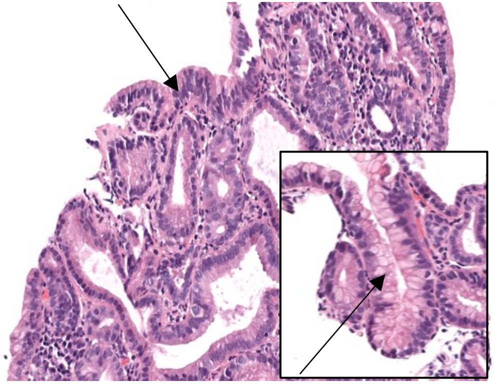


INTESTINAL-TYPE GASTRIC ADENOMA

- Localized polypoid lesion with **dysplastic intestinal-type epithelium**
- Polypoid dysplastic tubules lined by columnar epithelium showing intestinal differentiation (like colorectal adenomas) with varying degrees of Paneth and goblet cells
- Risk factors include **any cause of gastric intestinalization (e.g. H. pylori and autoimmune gastritis)** and genetic syndromes
- Third most common type of gastric polyp
- Intestinal type gastric adenoma is more prone to progress to gastric cancer than foveolar-type gastric adenoma

Path Presenter

Dysplastic foveolar epithelum with mucin-cap



Mucin-cap (differentiating feature)

FOVEOLAR-TYPE ADENOMA

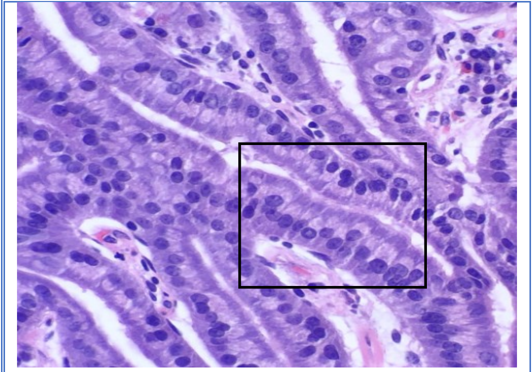
Path Presenter

MORPHOLOGY

- Polypoid lesion with dysplastic foveolar epithelium, mostly occurs in the oxyntic compartment (body/fundus)
- Dysplastic foveolar-type epithelium shows stratified nuclei and a **distinctive PAS-positive apical neutral mucin cap**
- Background gastric mucosa is usually without inflammation, atrophy, or metaplasia.

OTHER HIGH YIELD POINTS

- **Usually syndrome-associated like FAP and GAPPS**; may coexist with fundic gland polyps and pyloric gland adenomas, and their **rate of cancer progression is consistently low**
- Foveolar-type adenoma with hybrid phenotype (both intestinal and gastric differentiation) carries a higher risk of cancer progression



Polyp composed of chief cells only in the gastric body
Image courtesy of Dr. Adam L. Booth @ALBoothMD

OXYNTIC GLAND ADENOMA

Path Presenter

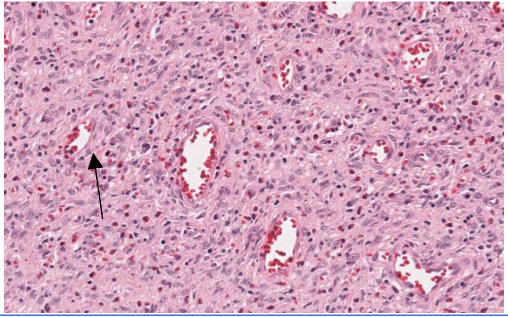
MORPHOLOGY

- Benign gastric neoplasm composed of columnar cells with pale basophilic cytoplasm and mild nuclear atypia, **mimicking oxyntic glands (mainly chief cells)**
- Occurs predominantly in the upper 1/3rd of the stomach and there is a high risk of progression to adenocarcinoma (gastric adenocarcinoma of fundic-gland type)
- IHC: Pepsinogen I and MUC6 (chief cell) and H+/K+ ATPase (parietal cell); MUC5AC negative

OTHER HIGH YIELD POINTS

- Missense or nonsense mutations in the **WNT/β-catenin signaling pathway** are seen

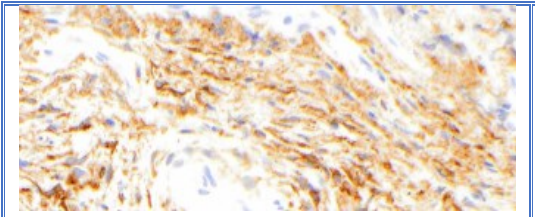
Spindle cells with onion skin arrangement around vessels



INFLAMMATORY FIBROID POLYP

MORPHOLOGY

- Benign lesion occurs throughout the gastrointestinal tract, **most commonly in the stomach**
- Characterized by **submucosal** proliferation of vascular fibrous tissue
- Bland spindle cells with characteristic **onion skin arrangement around small vessels**
- **Eosinophil rich** inflammatory infiltrate
- Edematous background
- IHC: **Positive expression for CD34** and consistently negative for CD117



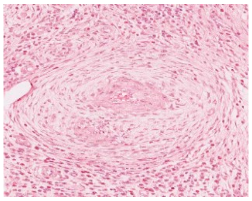
IHC: PDGFR-α positive

OTHER HIGH YIELD POINTS

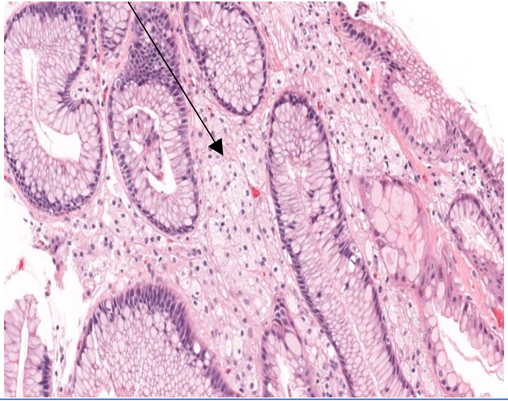
- Associated with **mutations in platelet-derived growth factor receptor-α (*PDGFRA*) gene** and PDGFR-α protein expression
- Good prognosis

Path Presenter

Onion skin arrangement



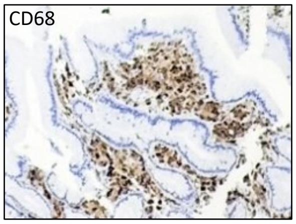
Bland foamy histiocytes in lamina propria



GASTRIC XANTHOMA

MORPHOLOGY

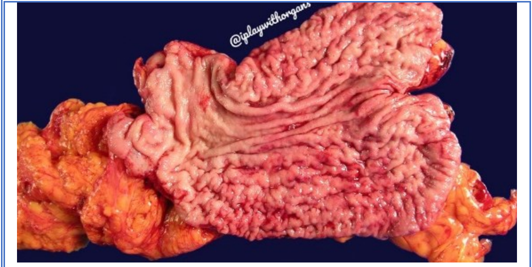
- Collection of bland **foamy histiocytes** in the lamina propria without mitotic activity and background inflammation
- Endoscopy: Single or multiple while/yellow nodule
- IHC: **CD68 positive** and negative for cytokeratin



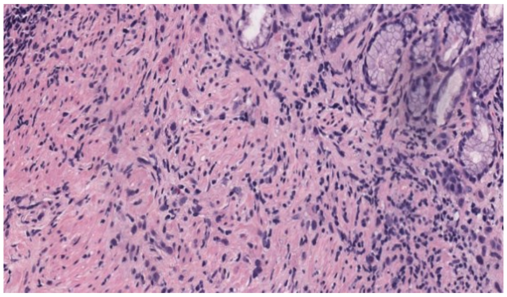
OTHER HIGH YIELD POINTS

- Associated with H.pylori infection, bile reflux, and **hypercholesterolemia**

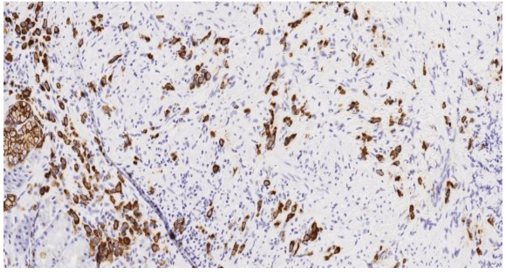
Path Presenter



Diffuse-type gastric cancer: Image credit: Cory Nash



Poorly cohesive carcinoma (non-signet ring cell type)



Cytokeratin IHC highlights tumor cells

GASTRIC ADENOCARCINOMA

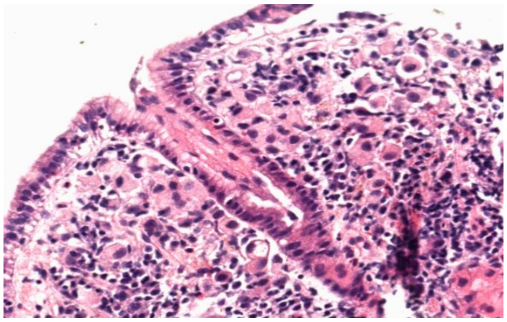
MORPHOLOGY

- Malignant epithelial neoplasm with invasion of lamina propria or beyond
- Early gastric carcinoma has three macroscopic subtypes

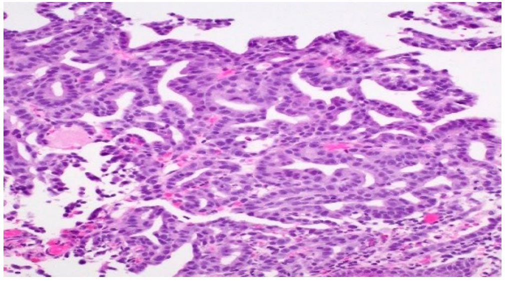
Type 0-I (Protruding)	**Polypoid lesions**
Type 0-IIa (Superficial elevated)	Slightly elevated/protruding
Type 0-IIb (Superficial flat)	No elevation or depression
Type 0-IIc (Superficial depressed)	Slightly depressed lesions
Type 0-III (Excavated)	Deeply depressed lesions

- Advanced gastric carcinoma is subtyped according to Borrmann classification
  - ➢ As localized growth with a fungating or ulcerated appearance or
  - ➢ As infiltrative growth with or without ulceration
- Linitis plastica or scirrhous carcinoma: Infiltrative growth with abundant fibrous stroma reaction resulting in thickened and rigid stomach wall
- Among the several histopathological classifications, Laurén and WHO classification are the widely accepted ones
- **Five main WHO histological subtypes** include: tubular, papillary, poorly cohesive (including signet-ring cell and other subtypes), mucinous, and mixed adenocarcinomas
- **Tubular adenocarcinoma:** Most common subtype, composed of dilated or slit-like branching tubules of variable diameter
  - ➢ Tumors with solid structures and barely recognizable tubules are classified as poorly differentiated tubular (solid) carcinoma
- **Poorly cohesive carcinoma (including signet-ring cell carcinoma and non-signet ring cell type):** Second most common type, composed of neoplastic cells that are isolated or arranged in small aggregates without well-formed glands
  - ➢ **Signet-ring cell type:** Composed predominantly or exclusively of signet-ring cells, which are characterized by a central, optically clear, globoid droplet of cytoplasmic mucin with an eccentric nucleus

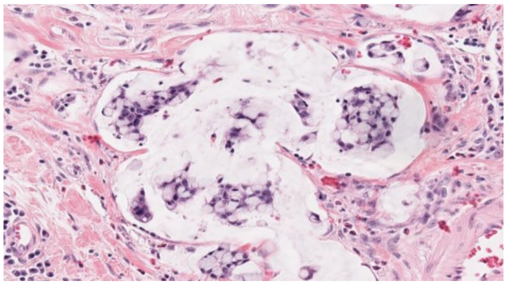
Poorly cohesive carcinoma (signet-ring cell type)



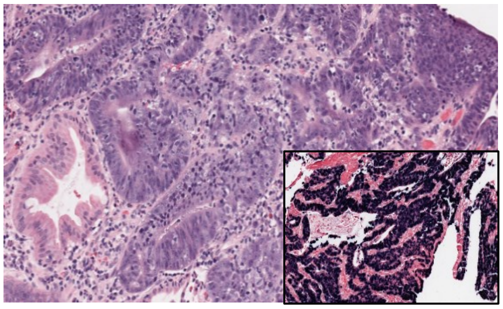
Tubular adenocarcinoma (gland-forming)



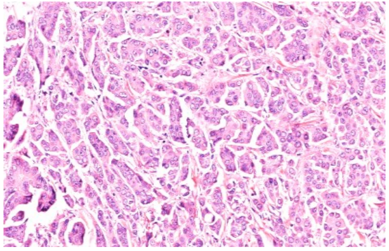
Mucinous adenocarcinoma



Adenocarcinoma with lymphoid stroma (EBER ISH)



Micropapillary carcinoma



Path Presenter

- Non-signet ring cell type: Composed of neoplastic cells resembling histiocytes or lymphocytes with deeply eosinophilic cytoplasm and pleomorphic nuclei
- **Mucinous adenocarcinoma:** Composed of malignant epithelium in extracellular mucin pools, with the latter accounting for > 50% of the tumor area; tumor cells may be in glands/tubules or single cells
- **Papillary adenocarcinoma:** Relatively rare subtype; shows an exophytic growth pattern with elongated finger-like processes lined by cuboidal or columnar cells supported by fibrovascular cores
  - Well-differentiated tumor with a pushing invasion and frequent infiltration by inflammatory cells
  - Associated with a higher frequency of liver metastasis and poor prognosis
- **Mixed adenocarcinoma:** Contains two or more distinct histological subtypes; often have a poorer prognosis than those with only one component
- **(Adeno)carcinoma with lymphoid stroma:** Also known as lymphoepithelioma-like carcinoma or medullary carcinoma
  - Characterized by irregular sheets, or ill-defined tubules, or syncytia of polygonal cells embedded in prominent lymphocytic infiltrate
  - Predilection for proximal stomach or gastric stump and often **EBV-associated** (better prognosis)
  - A subset of gastric carcinomas with **microsatellite instability (MSI)** have similar histological phenotype (better prognosis)
- **Hepatoid adenocarcinoma and related entities:** Composed of large polygonal eosinophilic hepatocyte-like neoplastic cells
  - Bile and PAS-D positive intracytoplasmic eosinophilic globules can be seen; Positive for AFP and HepPar-1
  - Other alpha-fetoprotein producing adenocarcinomas include papillary or tubular-type with clear cytoplasm, adenocarcinoma with enteroblastic differentiation, and yolk-sac tumor-like carcinoma
- **Micropapillary adenocarcinoma:** small clusters of tumor cells without fibrovascular cores protruding into clear spaces
  - Worse prognosis like micropapillary carcinomas in other organs
  - Proportion of micropapillary component required for the classification is not established
- **Gastric adenocarcinoma of fundic-gland type**: Very rare and assumed to develop from oxyntic gland adenoma
  - Three subcategories: chief cell-predominant (~99% of reported cases), parietal cell-predominant, and mixed phenotype
- By **Laurén classification:** Tumors are categorized as intestinal (tubular and papillary type in WHO), diffuse (poorly cohesive signet-ring cell and other type in WHO), and mixed type

OTHER HIGH YIELD POINTS

- Environmental risk factors include *H. pylori* (a strong risk factor which follows Correa's cascade: chronic infection→ chronic inflammation → intestinal metaplasia → dysplasia → carcinoma), EBV infection, tobacco smoking, and dietary factors
- Carcinoma involving the gastroesophageal junction with center ≤2 cm into the proximal stomach should be staged as esophageal cancer.
- Predictive biomarkers: **Anti-ERBB2 (HER2) therapy** benefits patients with unresectable or metastatic/recurrent ERBB2-positive carcinomas and **PD-L1 expression** is a biomarker of response to immune checkpoint inhibitor therapy

GASTRIC ADENOCARCINOMA

- Familial/hereditary setting includes ***CDH1* mutations in hereditary diffuse gastric cancer** and ***APC* exon 1B mutations in gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)**
- Four molecular subtypes are proposed by The Cancer Genome Atlas (TCGA):

EBV (~9%)

Gastric carcinoma with lymphoid stroma

Associated with CpG island (CIMP) and *CDKN2A* promoter hypermethylation pathway

Frequent *PIK3CA* and *ARID1A* mutations

PD-L1 and PD-L2 amplified

Better prognosis

Microsatellite Unstable (~22%)

Associated with MLH1, CpG island (CIMP) and *CDKN2A* promoter hypermethylation pathway

Better prognosis

Genomically Stable (~20%)

Poorly cohesive (diffuse) morphology

Overall fewer copy number alterations, however, frequent *CDH1* and *RHOA* alterations/mutations

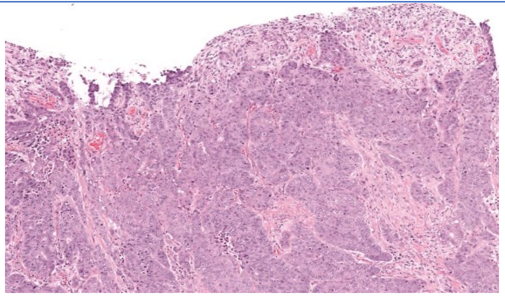
Poor prognosis

Chromosomally Unstable (~50%)

Predominantly intestinal type morphology

Frequent *TP53* mutations and amplifications of receptor tyrosine kinase (RTK)

Extensive DNA copy number variations



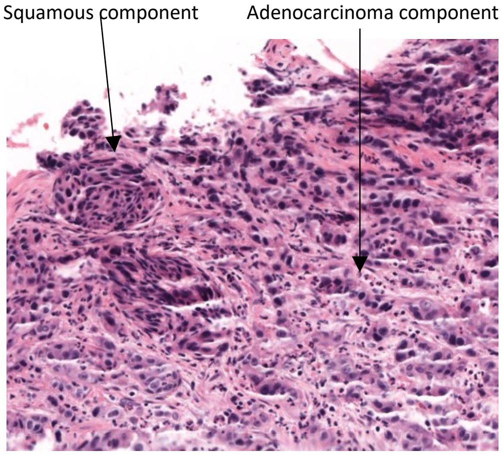
GASTRIC SQUAMOUS CELL CARCINOMA

MORPHOLOGY

- Malignant epithelial neoplasm with squamous cell differentiation, characterized by keratinocyte cells with intercellular bridges and/or keratinization

OTHER HIGH YIELD POINTS

- Very rare; extension from lower esophageal squamous cell carcinoma needs to be ruled out
- Frequently presents at an advanced stage and is associated with poor outcome



GASTRIC ADENOSQUAMOUS CARCINOMA

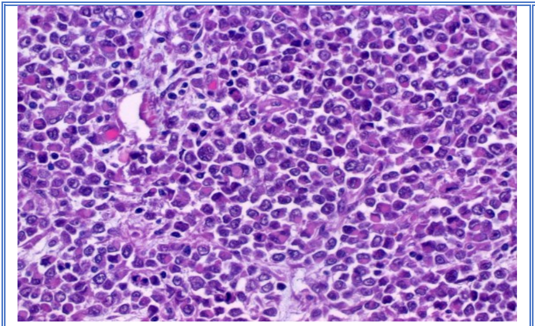
MORPHOLOGY

- Primary gastric carcinoma composed of both glandular and squamous cell components, with the squamous component constituting ≥ 25% of the tumor
- Mucin stain: Highlights glandular differentiation; p63/p40
- IHC: Helps determine the presence and extent of the squamous cell component

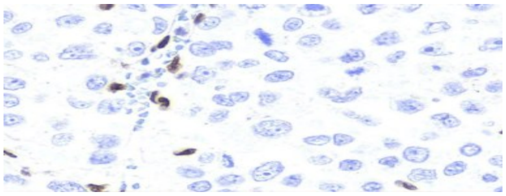
OTHER HIGH YIELD POINTS

- Very rare tumor
- Males more commonly affected (>60 years of age)
- Generally aggressive; tumor metastasis to regional lymph nodes, liver, and peritoneum are common

Path Presenter



Rhabdoid morphology of gastric undifferentiated carcinoma



BRG1 loss (*SMARCA4* gene)

GASTRIC UNDIFFERENTIATED CARCINOMA

MORPHOLOGY

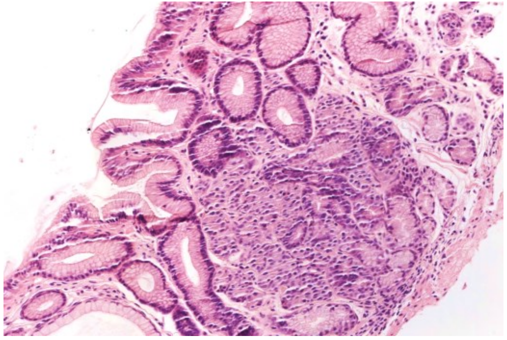
- Primary gastric carcinoma composed of anaplastic cells without specific cytological or architectural type of differentiation
- Diffuse sheets of anaplastic cells with variable cytology including polygonal, rhabdoid, spindled, sarcomatoid, carcinoma with osteoclast-like giant cells or carcinoma with lymphoepithelioma-like features
    - A glandular component may be observed and can vary from minimal to prominent; this suggests an origin via dedifferentiation
- IHC: Variable expression of pan-cytokeratin and consistent expression of vimentin; EMA may be helpful in keratin-poor tumor

OTHER HIGH YIELD POINTS

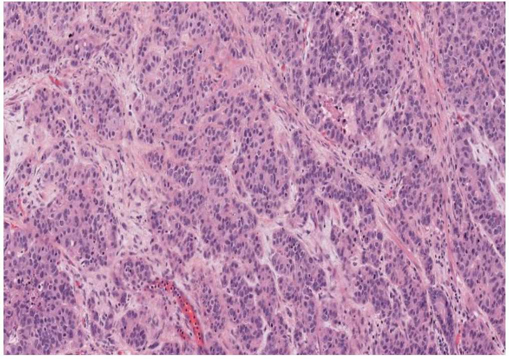
- Probably driven by various components of the **SWI/SNF chromatin-remodeling complex**
- Aggressive tumors; must rule out EBV-associated carcinoma with lymphoid stroma, aggressive lymphomas, melanoma, germ cell neoplasms, and sarcomas with epithelioid pattern

Path Presenter

Well-differentiated NET-Type 1



Well-differentiated NET-Type 3



GRADING OF NEUROENDOCRINE TUMORS

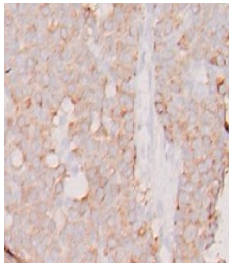
NET Grade (G)	Mitotic rate (per $2mm^2$)	Ki-67 index (%)
G1	<2	<3
G2	2-20	3-20
G3	>20	>20

GASTRIC NEUROENDOCRINE NEOPLASMS

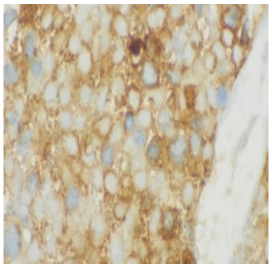
MORPHOLOGY

- Epithelial neoplasms with neuroendocrine differentiation, including well-differentiated neuroendocrine tumor (NET), poorly differentiated neuroendocrine carcinoma (NEC), and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
- NET: Composed of well-differentiated cells arranged in nests, acini, trabeculae, and ribbons, with abundant eosinophilic cytoplasm and monomorphic round nuclei (stippled/salt and pepper chromatin)
- Three main types of Enterochromaffin-like-cell (ECL-cell) NETs include
- **Type 1:** Associated with hypergastrinemia due to **chronic autoimmune atrophic gastritis**; autoantibody mediated destruction of parietal cells → achlorhydria → compensatory hyperplasia of antral G-cells (to try to signal to make more acid) → secrete gastrin → ECL cell hyperplasia and NET formation
    - **Most cases are grade 1 or 2 (G1 or G2),** with very rare incidence of G3 tumors
- Type 2: Associated with **Zollinger-Ellison syndrome** (hypergastrinemia) due to duodenal or pancreatic gastrinoma
- Type 3: **Sporadic**, grade ranges from G1-G3, however, often with **higher metastasis rate and tumor stage**
- Serotonin-producing EC-cell NET: Rare subtype and usually nonfunctional
- Gastrin-producing G-cell NET: Usually non-functioning, but may cause Zollinger–Ellison syndrome and those functional tumors are referred as “gastric gastrinoma”
- Somatostatin-producing D-cell NET: Positive for somatostatin
- NEC: Composed of poorly formed trabeculae or sheets of poorly differentiated cells, and are subtyped as small cell and large cell NEC
    - Small cell NEC: Cells with scant cytoplasm, hyperchromatic nuclei with molding and absent nucleoli
    - Large cell NEC: Large cells with abundant eosinophilic cytoplasm, vesicular nuclei showing prominent nucleoli.
- NECs typically feature mitotic count of $>20/mm^2$ and Ki-67 proliferation index frequently >60-70%

Synaptophysin



CD56



- Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN): Mixed adenocarcinoma-NEC (MANEC), mixed adenocarcinoma-NET, and mixed adenoma-NET are seen

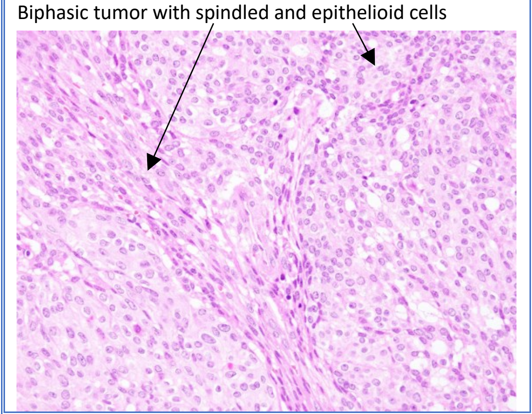
OTHER HIGH YIELD POINTS

- ***TP53* and *RB1*** mutations can help distinguish NEC from G3 NET (wild-type in NET)
- Prognosis of NENs depends on tumor type, grade, and stage

Path Presenter

	Type 1	Type 2	Type 3
Cause	Autoimmune gastritis	Zollinger-Ellison syndrome, often MEN1 syndrome	Sporadic
Demographic	More frequent in females	No sex predilection	More frequent in males
Focality	Multifocal	Multifocal	Solitary
Arises from	ECL-cell (body/fundus)	ECL-cell (body/fundus)	ECL, EC, G & D-cells (anywhere)
Frequency	80-90%	5-7%	10-15%
Hypergastrinemia	Yes (secondary)	Yes (Primary)	No
ECL-cell proliferation	Yes	Yes	No
Acid secretion	Low or absent	High	Normal
Background mucosa	Atrophic gastritis	Parietal cell hyperplasia	Normal
Stage at diagnosis	Most are low stage	Usually, low stage	Often advanced
5-year survival	~100%	60-90%	<50%

Biphasic tumor with spindled and epithelioid cells



GASTROBLASTOMA

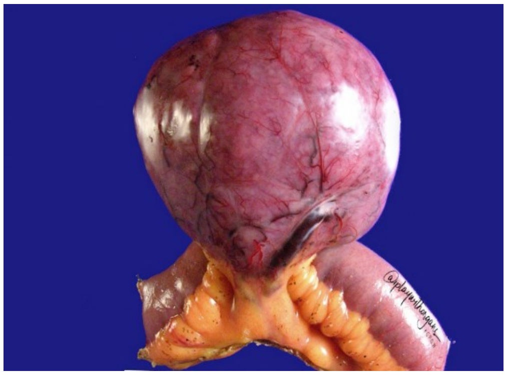
MORPHOLOGY

- Biphasic tumor consisting of uniform spindle cells and epithelial cells arranged in nests, arising in the gastric muscularis propria
- IHC: Epithelial component expresses pan-cytokeratins and focal CD56 and CD10; spindle cell component is negative for keratins but positive for CD56 and CD10; negative for C-KIT, DOG1, CD34, SMA, desmin, synaptophysin, chromogranin, and S100

OTHER HIGH YIELD POINTS

- Characteristic gene fusion: *MALAT1-GL1*

Path Presenter



GIST in the small bowel in this image: Well-circumscribed lesion

GASTROINTESTINAL STROMAL TUMOR (GIST)

MORPHOLOGY

- Mesenchymal neoplasm characterized by differentiation towards **interstitial cells of Cajal** and can occur anywhere in the gastrointestinal tract
- Gross: Usually well circumscribed mass of variable size, centered within muscularis propria
- Microscopy: Most gastric GISTs are spindle cell type, epithelioid morphology in 20-25% cases, and some feature mixed phenotype

- **Spindle cell type:** Usually arranged in diffuse sheets or vague storiform pattern, cells with eosinophilic cytoplasm (can have cytoplasmic vacuoles), and rare nuclear pleomorphism
  - Distinct histologic patterns include sclerosing, palisaded-vacuolated (most common type), diffuse hypercellular, and sarcomatous type (with nuclear atypia and high mitosis)

  - Small intestinal and colonic GISTs are usually spindle cell type, and those with low biological potential often contain skenoid fibers (extracellular collagen globules)

- **Epithelioid GIST:** Clear to eosinophilic cytoplasm, may show sclerosing, discohesive, hypercellular or sarcomatous morphology with substantial atypia and mitotic activity
  - **SDH-deficient GISTs characteristically show epithelioid morphology,** gastric location, multinodularity, increased chance of lymphovascular invasion, and lymph node metastasis

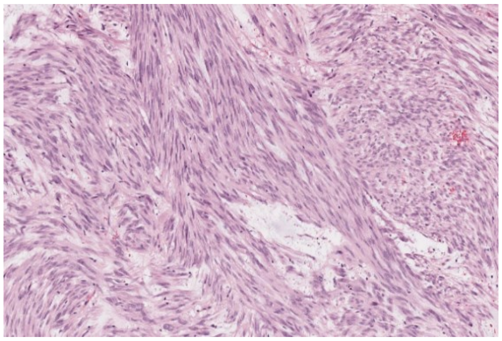
- **Dedifferentiated GIST:** Progression to high-grade (KIT-negative) sarcomatous morphology observed either de novo or after therapy with imatinib
  - Can be associated with heterologous epithelial, myogenic, or angiosarcomatous differentiation
- IHC: Most tumors are diffusely positive for **C-KIT (CD117)**; **DOG1/ANO1**-equally sensitive and specific as C-KIT, reactive in ~50% of C-KIT negative GISTs; **CD34**- Most spindle cell types (especially gastric) are positive
- SDH-deficient GISTs exhibit loss of SDHB protein expression irrespective of which SDH gene is mutated

OTHER HIGH YIELD POINTS

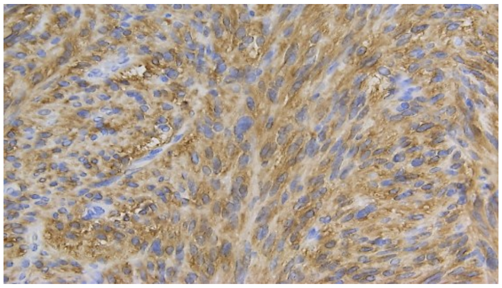
- ~54% GISTs arise in the stomach, 30% in the small intestine, 5% in the colon and rectum, and about 1% in the esophagus
- About 75% of GISTs harbor gain-of-function mutations of the *KIT* (most often in exon 11 or exon 9) and 10% harbor *PDGFRA* activating mutations
  - Both oncogenes are located on chromosome 4, encoding for type III receptor tyrosine kinases
  - The mutations are mutually exclusive and result in the constitutive activation of either KIT or PDGFRA
- Many GISTs that are wildtype for *KIT* and *PDGFRA* harbor alterations in SDH subunit genes, leading to SDH dysfunction
  - SDH-deficient GISTs usually occur in younger patients and nearly all pediatric GISTs are SDH-deficient
- Majority are sporadic and 5-10% GISTs arise in the setting of various syndromes
- Most syndromic GISTs are SDH-deficient which includes
  - **Carney triad** (GIST, pulmonary chondroma, paraganglioma); non-hereditary disorder and usually show *SDHC* promoter methylation
  - **Carney–Stratakis syndrome** (GIST and paraganglioma); autosomal dominant disorder with SDH germline mutation.
- Neurofibromatosis type 1 (NF1) patients rarely develop GIST; often multifocal and most are in small intestine
- Familial GISTs (extremely rare) are caused by germline mutations of *KIT* or *PDGFRA*, and usually are multifocal with aggressive behavior
- Most important prognostic parameters for GIST are mitotic activity, tumor size, and anatomical location
  - Tumor rupture is an adverse factor

Path Presenter

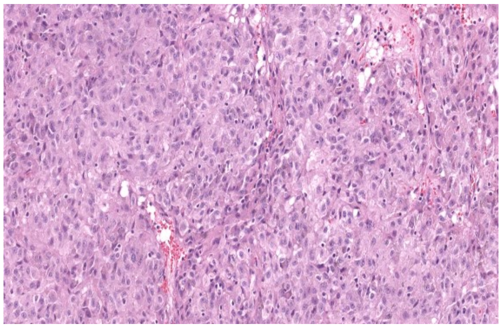
GIST- Spindle cell type



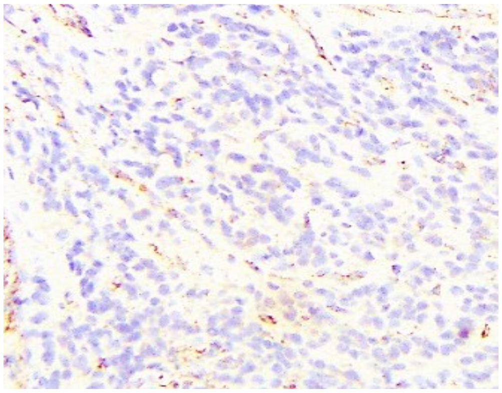
CKIT Positive



GIST: Epithelioid type

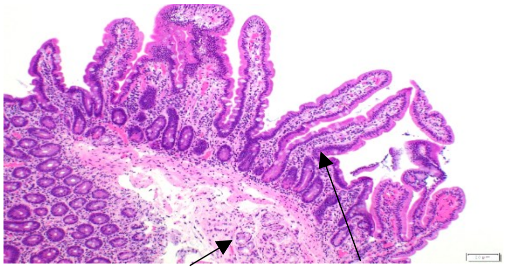


SDHB immunohistochemical stain showing loss of expression in epithelioid GIST



5. GASTROINTESTINAL PATHOLOGY

SMALL BOWEL: NORMAL



- **Duodenum:** Villi and submucosal Brunner mucus glands are identifiable features
- Duodenum is 25-30 cm long, C-shaped, and located in the upper abdomen
- Head of the pancreas lies in the C-loop
- Duodenum is divided into four sections: superior, descending, horizontal, and ascending
- Villus to crypt ratio: 3-5:1

SMALL INTESTINE ASSOCIATIONS

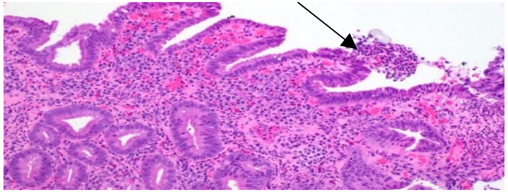
Villi	Blunt with Celiac Disease
Goblet cells/Paneth cells	Missing in autoimmune enteropathy
Intraepithelial lymphocytes	Increased in Celiac, peptic injury, infections, small bowel overgrowth
Plasma cells	Absent in immunodeficiency
Critters	Look in between villi and surface
Vessels	Look for amyloid and vasculitis
Endocrine cells	Absent in endocrine dysgenesis

- **Jejunum and Ileum:** Tallest villi in the jejunum; ileum can appear nodular due to Peyer's patches; no Brunner glands in the jejunum and ileum
- Entire small bowel has the following layers: Mucosa (includes lamina propria, epithelium, and muscularis mucosae), submucosa (blood vessels and fibroadipose tissues), muscularis propria (inner circular and outer longitudinal smooth muscle), subserosa, and serosa

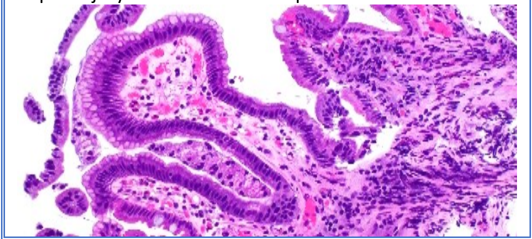
Path Presenter

SMALL BOWEL: NON-NEOPLASTIC

Acute duodenitis with neutrophils in the epithelium



Peptic injury with foveolar metaplasia



ACUTE DUODENITIS

MORPHOLOGY

- **Neutrophils in the duodenal epithelium**

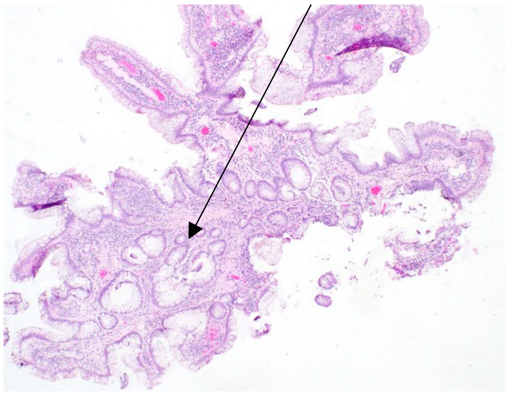
OTHER HIGH YIELD POINTS

ETIOLOGIES

- **Infection: Most common with *Helicobacter pylori*; can lead to ulcers**; other etiologies include adenovirus, cytomegalovirus
- **Peptic duodenitis:** Acute inflammation + gastric foveolar metaplasia + Brunner gland hyperplasia; seen with excess gastric acid and/or *Helicobacter pylori*
- **Medications**: NSAIDs commonly
- **Inflammatory bowel disease**: Crohn disease can affect the duodenum

Path Presenter

Architectural distortion



CHRONIC INJURY IN INFLAMMATORY BOWEL DISEASE

MORPHOLOGY

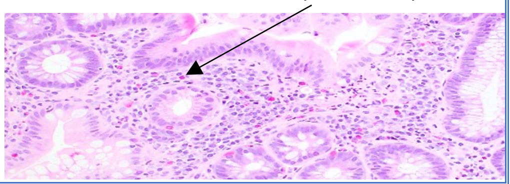
- **Architectural distortion** - Crypt branching and drop-out
- **Pyloric metaplasia**
- Often with villous blunting and basal plasmacytosis
- Also see acute inflammation (cryptitis and crypt abscesses)
- Look for granulomas and transmural inflammation in resection specimens

OTHER HIGH YIELD POINTS

- Particularly in Crohn disease in the terminal ileum

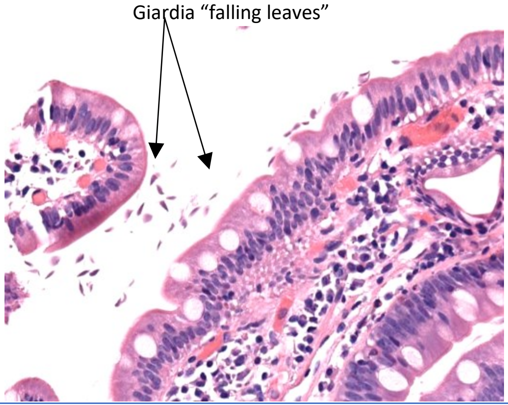
Path Presenter

Pyloric metaplasia



5. GASTROINTESTINAL PATHOLOGY

INFECTIONS



Giardia "falling leaves"

GIARDIA

MORPHOLOGY

- Characteristic trophozoites are **pear-shaped, binucleate, faintly basophilic organisms** seen in between villi with no associated inflammation
- Sometimes mild villous blunting and intraepithelial lymphocytes can be seen
- Look like **"falling leaves"** in the bowel lumen

Path Presenter

OTHER HIGH YIELD POINTS

- **Most common protozoa infection in the United States**
- Usually acquired from contaminated water; can be fecal-oral and sexually transmitted
- More common in children, with travel, and immunocompromised
- Causes diarrhea (unclear pathogenesis), often watery and foul-smelling
- Infection can be chronic in immunocompromised

Organisms are located at the apex of epithelial cells along the luminal border

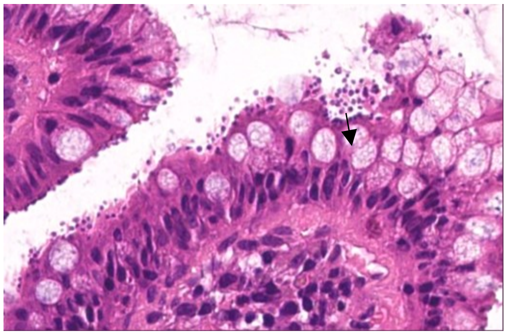


Image credit: Dr. Megan Smith, Twitter @megothelioma

CRYPTOSPORIDIA

Path Presenter

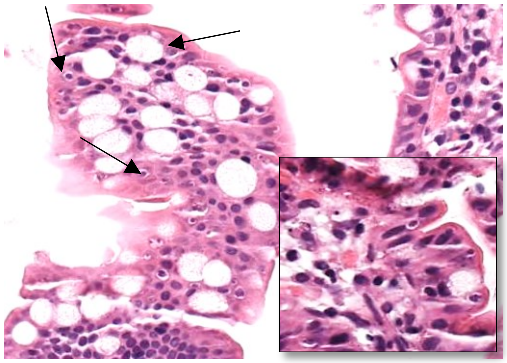
MORPHOLOGY

- Protozoal Parasite-Cryptosporidium species, most common ***C. hominis and C. parvum***
- Organisms are **2-5 µm** in diameter and **located at apex of epithelial cells along the luminal border**, basophilic on H&E
- Villous blunting with mixed inflammatory infiltrate may be seen
- Positive for modified AFB

OTHER HIGH YIELD POINTS

- Small bowel is the most common site
- Other organs: colon, stomach, biliary tree, respiratory tract
- Clinical presentation: In immunocompetent hosts, self-limited profuse diarrhea (1-2 days); in immunocompromised, debilitating symptoms

Round forms of Cyclospora, perinuclear and intracellular



CYCLOSPORA

MORPHOLOGY

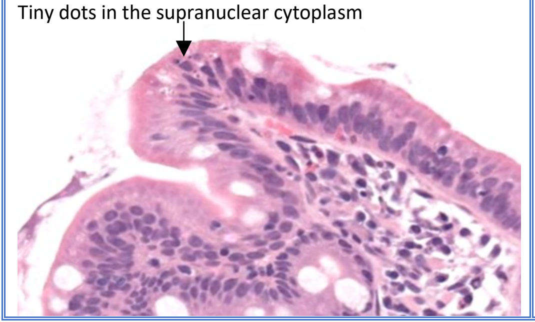
- *Cyclospora cayetanensis* is the only species that infects humans
- Round forms: **2-3 µm**; crescentic merozoites: 5-6 µm
- **Intracellular, within the upper 1/3rd of the epithelium**; parasitophorous vacuoles

OTHER HIGH YIELD POINTS

- Foodborne and waterborne intestinal parasite
- Infection is mild to asymptomatic; treated with Bactrim
- Endemic in tropics and subtropical regions of Latin America, Central and Southeast Asia, Middle East, and North Africa

Path Presenter

Tiny dots in the supranuclear cytoplasm



MICROSPORIDIA

Path Presenter

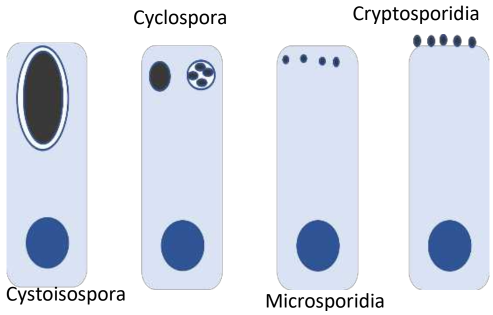
MORPHOLOGY

- Caused by *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*
- Small spores **(2-3 µm) in the supranuclear cytoplasm in epithelial cells** and lamina propria macrophages
- Minimal to no changes in the mucosa

OTHER HIGH YIELD POINTS

- Causes chronic diarrhea in immunocompromised patients
- Diagnosis by stool examination, polymerase chain reaction (PCR)

Intestinal cell with varying protozoan infections: Size, location, and morphology



CYTOISOSPORA (ISOSPORA)

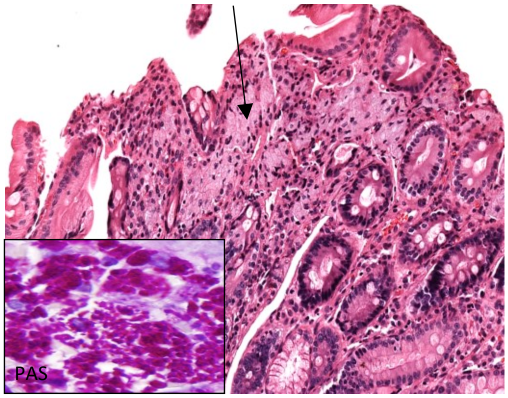
MORPHOLOGY

- Opportunistic infection by protozoan parasite ***Cystoisospora belli*** (formerly known as *Isospora belli*)
- Large, **20-33 µm in length and 10-19 µm in width, perinuclear/subnuclear**
- Intraepithelial inclusions that infect epithelial cells and macrophages
- Schizonts and merozoites are crescent-shaped
- Sexual forms are round with prominent nucleus and nucleolus
- Parasitophorous vacuoles

OTHER HIGH YIELD POINTS

- Causes diarrhea and weight loss

Foamy macrophages in duodenal lamina propria (PAS)



WHIPPLE DISEASE

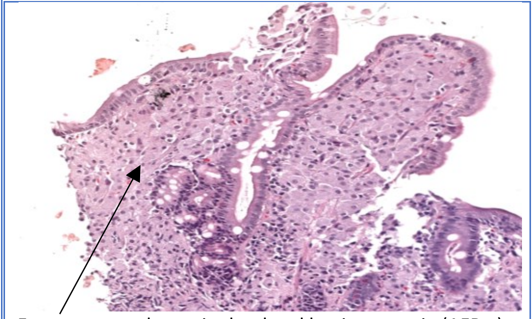
MORPHOLOGY

- Rare bacterial infection caused by ***Tropherma whipplei*** often diagnosed on small bowel biopsies
- Lamina propria expanded by a **foamy macrophage infiltrate**, diffuse or patchy
- **PAS/PAS-D positive**: granular particles that appear sickle-shaped

OTHER HIGH YIELD POINTS

- Affect small intestine>esophagus>stomach> appendix>colon
- Symptoms of malabsorption, diarrhea, arthralgias, pain, and neurological symptoms
- Differential diagnosis: *Mycobacterium avium intracellulare complex* (PAS negative, AFB positive)

Path Presenter



Foamy macrophages in duodenal lamina propria (AFB +)

MYCOBACTERIUM AVIUM COMPLEX (MAC)

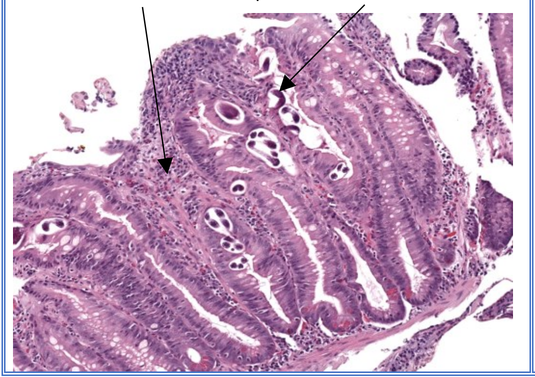
MORPHOLOGY

- Expansion of lamina propria by **foamy macrophages** containing MAC (**FITE and AFB positive, PAS negative**)

OTHER HIGH YIELD POINTS

- Seen in immunocompromised patients
- Differential diagnosis: Whipple disease (PAS positive, FITE/AFB negative); mycobacterium tuberculosis causes necrotizing granulomatous inflammation

Path Presenter



STRONGYLOIDES

Path Presenter

MORPHOLOGY

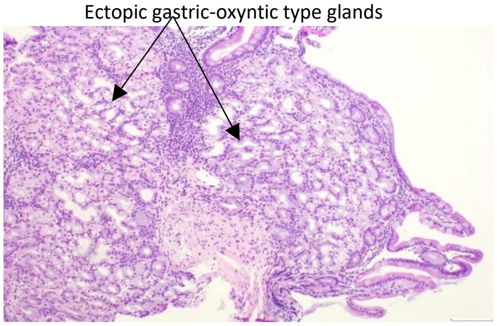
- Nematode infection that affects **immunocompromised people**
- **Adult worms, larvae, and eggs** can be found in crypts
- Inflammation with neutrophils and **often eosinophils**, may resemble inflammatory bowel disease

OTHER HIGH YIELD POINTS

- Worldwide distribution; very common in the tropics and the southeast United States
- Often get through the skin when barefoot on contaminated soil
- Skin→Lung→GI tract→Feces→Next host (or autoinfect)
- Female lives and lays eggs in the small intestine
- Can be asymptomatic; when symptomatic- diarrhea, pain, and bleeding

5. GASTROINTESTINAL PATHOLOGY

SMALL BOWEL: NON-NEOPLASTIC



ECTOPIC/HETEROTOPIC TISSUE

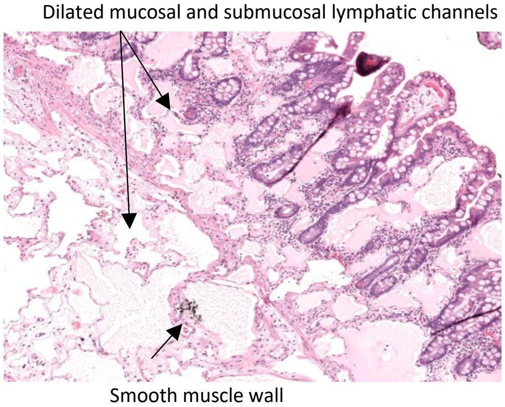
Path Presenter

MORPHOLOGY

- Ectopic/heterotopic tissue implies **presence of tissue type in a non-physiological site**
- **Gastric and pancreatic heterotopic tissue** can be found in the small bowel
- In gastric tissue, one can see foveolar epithelium with antral glands or oxyntic glands with parietal and chief cells
- In pancreatic tissue, one can see acini, duct, and/or islet cells

OTHER HIGH YIELD POINTS

- **Can form a mass lesion/polyp**; symptoms can range from abdominal pain, obstruction, intussusception, and perforation to asymptomatic



LYMPHANGIECTASIA/LYMPHANGIOMA

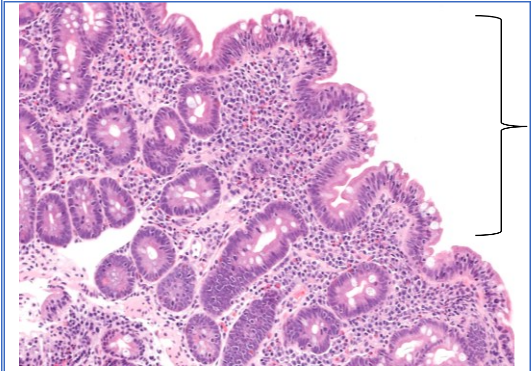
Path Presenter

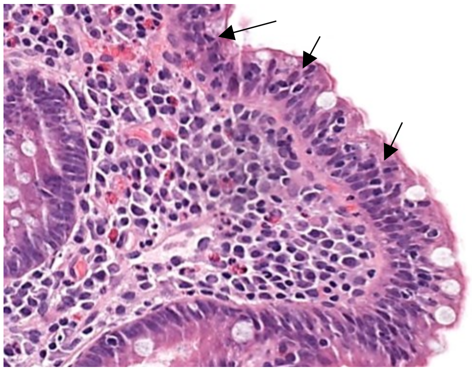
MORPHOLOGY

- **Lymphangiectasia:** Dilated mucosal and submucosal lymphatic vessels without mass formation; can be primary or secondary
- **Lymphangioma:** Mass forming lesion of dilated lymphatic channels in loose connective tissue stroma; may have smooth muscle wall and lymphoid aggregates
- Positive for CD34, CD31, D2-40, and Factor 8

OTHER HIGH YIELD POINTS

- Lymphagiectasia can be primary or secondary; primary more common in children; can lead to diarrhea and protein-losing enteropathy if extensive; secondary due to obstruction, tumor, adhesions, stricture, prior surgery; need to exclude malignancy
- Lymphangioma is a benign lesion


Blunted villi


Increased intraepithelial lymphocytes

CELIAC SPRUE/GLUTEN-SENSITIVE ENTEROPATHY.

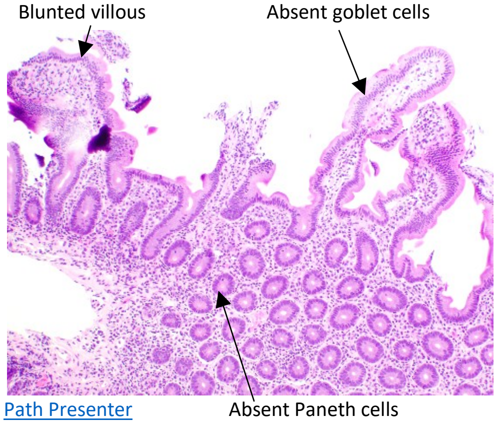
Path Presenter

MORPHOLOGY

- **Villous atrophy**, decreased villous to crypt ratio
- **Increased intraepithelial lymphocytes (IELs)**, typically >20 lymphocytes/100 enterocytes; "Crescendo" at tip of villi
- Scalloped villi may be seen endoscopically
- CD3 immunohistochemical stain can highlight IELs if needed

OTHER HIGH YIELD POINTS

- **Gluten exposure** triggers inflammation, primarily in the duodenum; causes diarrhea clinically often with weight loss
- Positive serology for **Antigliaden, Tissue Transglutaminase (TTG), and Antiendomysial (EMA) antibody** (if not IgA deficient)
- Associated with haplotypes **HLA-DQ2 or DQ8**; absence of both essentially excludes the diagnosis
- **Increased risk of malignancy** (small intestinal T-cell lymphoma and adenocarcinoma)
- May be associated with lymphocytic colitis/gastritis
- Differential diagnosis for increased intraepithelial lymphocyte with/without blunting: Tropical sprue, collagenous sprue, peptic injury, infection, medications, autoimmune enteropathy, and bacterial overgrowth
- **Tropical sprue:** post-infectious; after traveling to Africa, Asia, or South America; similar histology to Celiac
- **Collagenous sprue:** May be a component of refractory sprue; lacks auto-antibodies and may not respond to gluten-free diet; similar histology to Celiac
- **Bacterial overgrowth:** Diagnosis >100,000 colony-forming units/mL in culture (small bowel fluid aspirate)

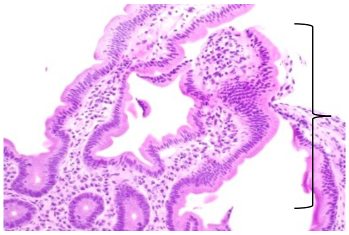


Path Presenter

AUTOIMMUNE ENTEROPATHY

MORPHOLOGY

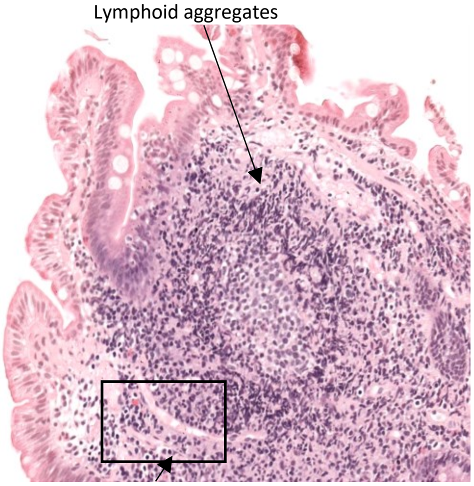
- **Diminished/absent goblet cells and Paneth cells** (not required for diagnosis)
- Villous blunting, increased intraepithelial lymphocytes, increased crypt apoptosis



Absent goblet cells

OTHER HIGH YIELD POINTS

- Intractable diarrhea
- Presents at **infancy and early age**
- Multifactorial; associated with Immune dysregulation, polyendocrinopathy, Enteropathy, X-linked (IPEX syndrome); Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED) syndrome; IPEX-like syndrome
- Extraintestinal manifestations: diabetes, autoimmune hepatitis, alopecia, ectodermal dystrophy, candidiasis, hypothyroidism
- Exact pathogenesis is unclear: **anti-enterocyte and anti-goblet cell antibodies**



Lamina propria devoid of plasma cells

COMMON VARIABLE IMMUNODEFICIENCY

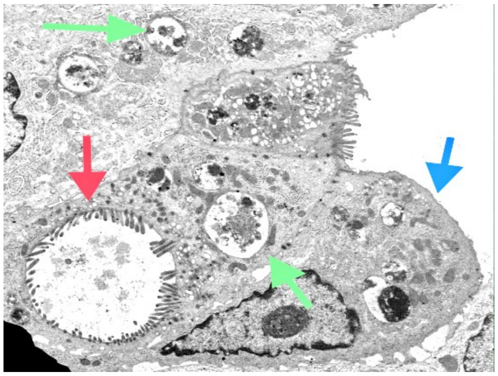
Path Presenter

MORPHOLOGY

- Immunodeficiency disorder with characteristic histologic feature of **absence of plasma cells in the lamina propria** (not required for diagnosis as they can be present in some cases)
- Lymphoid aggregates, mild villous blunting, increased intraepithelial lymphocytes
- Often find other infectious agents such as Giardia

OTHER HIGH YIELD POINTS

- **Second most common immunodeficiency disorder** after selective IgA deficiency
- Age of onset varies from childhood to adulthood with a bimodal peak age in the first and third decades
- B-cell impairment causing **hypogammaglobulinemia** with IgA or IgM deficiency and reduced immunoglobulins lead to **increased susceptibility to infections** especially sinopulmonary and gastrointestinal infections



Electron microscopy (EM): Loss of surface microvilli (blue arrow), cytoplasmic inclusions with immature microvilli (red arrow), and abnormal vacuoles (green arrow)

MICROVILLOUS INCLUSION DISEASE (MVID)

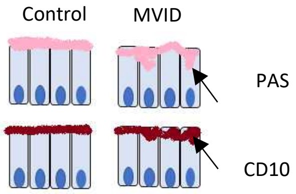
MORPHOLOGY

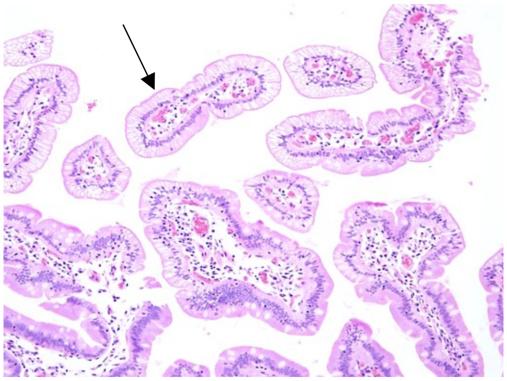
- Accumulation of PAS-positive granules at the apical pole of immature enterocytes, together with atrophic band indicating microvillous atrophy
- **CD10 and PAS stain positive within the enterocytes (cytoplasmic staining) versus just linear brush border staining in normal controls** (see pictorial depiction below)

OTHER HIGH YIELD POINTS

- **Congenital intestinal disorder** characterized by **severe, watery diarrhea** and an inability of the intestine to absorb nutrients
- No treatment exists for MVID; rarely live beyond two years of age

EM image courtesy of Dr. Vighnesh Walavalkar, Twitter @vighnesh_w, used with permission





Fat vacuoles in apical villous cytoplasm

ABETALIPOPROTEINEMIA

MORPHOLOGY

- Mutation in ***MTP* gene** encoding Microsomal Triglyceride Transfer Protein (MTTP); autosomal recessive
- Causes defect in synthesis and export of apoprotein B for intestinal mucosal cells; leads to **fat vacuoles in the villous epithelium**

OTHER HIGH YIELD POINTS

- Symptoms: failure to thrive, diarrhea, steatorrhea
- Free fatty acids and monoglycerides cannot assemble in chylomicrons and becomes triglycerides in cells causing cytoplasm vacuolization
- CBC with **acantholytic cells (burr cells)** and **lipid profile shows no chylomicrons, no VLDL, and no LDL**

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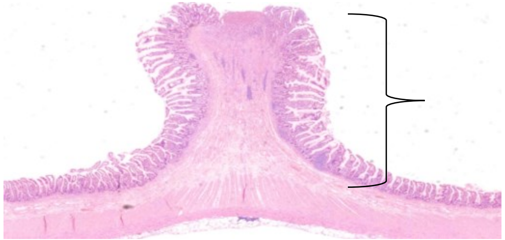
Image courtesy of Dr. Juan Putra @path_putra

Thin circumferential membrane composed of mucosa, submucosa, and fibrosis



Gross image courtesy of Dr. Trupti Mandalia, @Pathmath1, used with permission

DIAPHRAGM DISEASE

MORPHOLOGY

- **Thin circumferential membranes** similar to plicae circularis, composed of **mucosa and submucosa with fibrosis**
- Causes **strictures**; also see ulcers and even perforation

OTHER HIGH YIELD POINTS.

- **Related to NSAIDs use**
- Involves the small bowel

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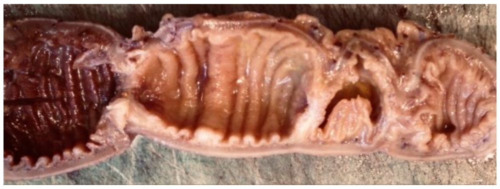
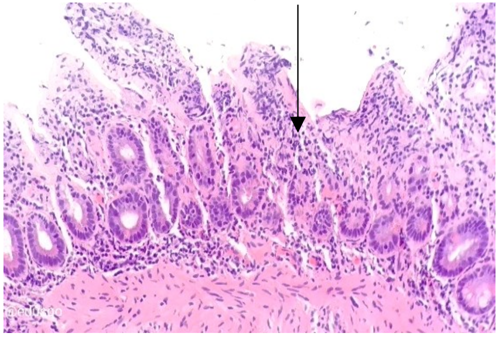


Thickened subepithelial collagen band



OLMESARTAN ENTEROPATHY

MORPHOLOGY

- A sprue-like enteropathy associated with **Olmesartan** and to a lesser degree another angiotensin II receptor antagonists
- Variable morphology from **increased intraepithelial lymphocytes and villous blunting to thickened subepithelial collagen**

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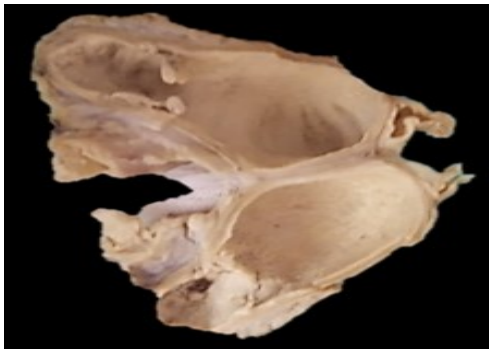
OTHER HIGH YIELD POINTS

- Mainly **affects the duodenum**
- **Negative celiac serologies**
- Clinical symptoms of diarrhea that resolve with discontinuation of medication
- Differential diagnosis: Rule out celiac disease

Image courtesy of Dr. Anju Pandey @anjuthevirgo



ENTERIC DUPLICATION CYST

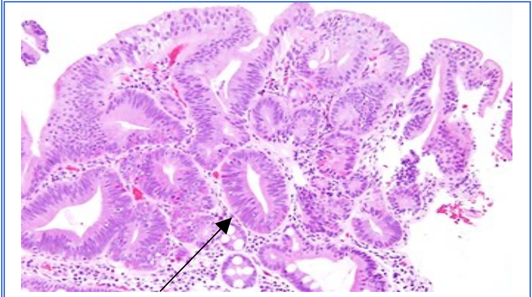
MORPHOLOGY

- **Cystic outpouching that looks similar histologically to the normal bowel wall and has a shared muscle layer**
- Can occur anywhere throughout the GI tract, **most common in the ileum** in the small bowel
- Can be associated with gastric heterotopia

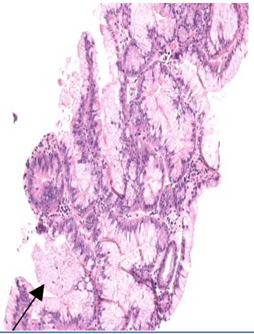
OTHER HIGH YIELD POINTS

- Pathogenesis: Developmental abnormality with abnormal luminal recanalization
- Can present with symptoms of pain, nausea/vomiting, and gastrointestinal bleeding

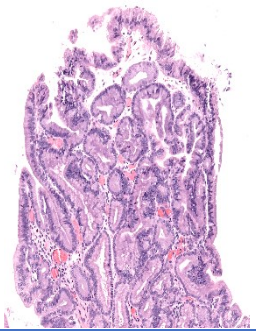
SMALL BOWEL: NEOPLASTIC


Intestinal type: Pencillate hyperchromatic nuclei

Apical mucin (foveolar)



Pyloric gland adenoma



ADENOMA

MORPHOLOGY

- **Intestinal type:** Similar to tubular adenoma of colon with "picket-fence nuclei:" elongate, pseudostratified, and hyperchromatic
- Nuclei remain in basal location in low grade dysplasia while high grade dysplasia shows cytologic pleomorphism, prominent nucleoli, architectural complexity, intraluminal necrosis, and no breach of basement membrane
- **Foveolar adenoma:** Tubulovillous architecture, tall columnar epithelium that resembles gastric foveolar cells and has a characteristic mucinous cap; prone to harbor high-grade dysplasia
- **Pyloric gland adenoma:** Tightly packed tubules that are lined by a monolayer of cuboidal cells that have granular t eosinophilic to ground glass cytoplasm; no apical mucin cap

OTHER HIGH YIELD POINTS

- Within the small intestine, duodenum is predisposed to developing adenomas
- Mean age of diagnosis is 65 years, with a slight male predilection
- Non-ampullary duodenal adenomas (~60%) are associated with Familial Adenomatous Polyposis (FAP) or MUTYH- Associated Polyposis

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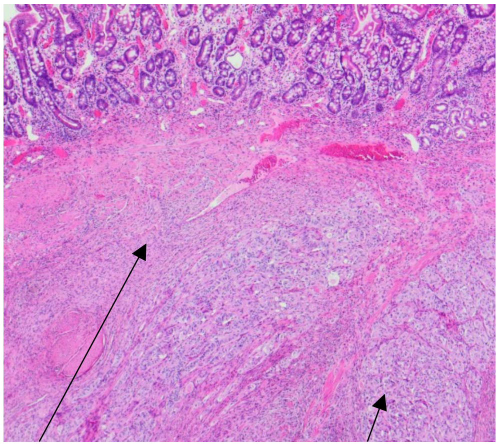

GANGLIOCYTIC PARAGANGLIOMA

MORPHOLOGY

- Three characteristic cell types: **epithelioid, spindle-shaped, and ganglion-like**
- IHC: Epithelioid cells: CD56, synaptophysin, chromogranin-A, somatostatin, progesterone receptor, pancreatic polypeptide
- Ganglion cells: S100, CD56, synaptophysin, chromogranin-A, somatostatin, pancreatic polypeptide
- Spindled cells: S100, BCL2

OTHER HIGH YIELD POINTS

- **Rare tumor of the periampullary region and the second part of the duodenum**
- **Usually benign,** however, ~7% can metastasize
- Unencapsulated submucosal lesion

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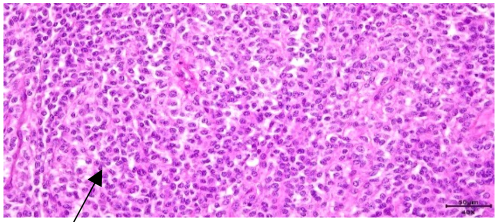
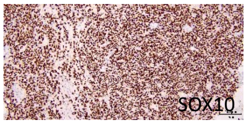
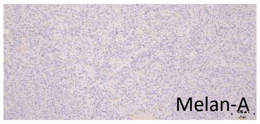
Images courtesy of Dr. Phoenix Bell, Twitter @PhoenixBell, used with permission


Monotonous tumor cells with prominent nucleoli





MALIGNANT GASTROINTESTINAL (GI) NEUROECTODERMAL TUMOR/CLEAR CELL SARCOMA-LIKE TUMOR OF THE GI TRACT

MORPHOLOGY

- Malignancy with **sheets** of **monotonous tumor cells, macronucleoli,** scanty cytoplasm, and conspicuous mitoses
- Nested, solid, pseudopapillary, pseudoalveolar, microcystic, rosette-like architecture; osteoclast-like giant cells can be seen
- IHC: Positive for **S100, SOX10, synaptophysin,** and vimentin while negative for **HMB45, Melan-A,** CD117, DOG1, **cytokeratin**

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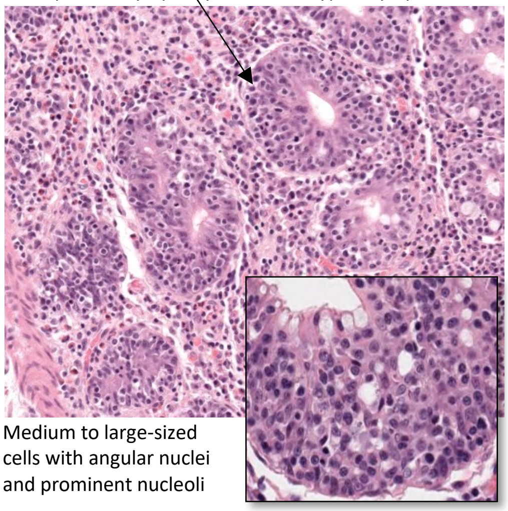
OTHER HIGH YIELD POINTS

- Small bowel is the most common site in GI tract; Median age: 35 years; M=F
- Translocation has ***EWSR1* rearrangement (*EWSR1- ATF1*[t(12;22)] or *EWSR1-CREB1*)**

Intraepithelial lymphocytosis with atypical lymphoid cells



Medium to large-sized cells with angular nuclei and prominent nucleoli

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

MORPHOLOGY

- Features of celiac disease with **increased intraepithelial lymphocytes**, crypt hyperplasia, and villous atrophy
- Lesion with **pleomorphic infiltrate of medium to large sized neoplastic cells** with prominent nucleoli, angulated nuclei, anaplasia, mitotic figures, and necrosis
- IHC: Positive for CD3, CD7, TIA, Perforin, granzyme B, CD103, and CD30; negative for CD20, EBER; **loss of some T cell markers such as CD2, CD4, CD5, and CD8**

OTHER HIGH YIELD POINTS

- **T-cell lymphoma that occurs in Celiac disease** and affects the intestine; jejunum >ileum/duodenum
- Stronger association with refractory disease
- Rare bone marrow, other viscera, and large intestine involvement
- Clonal *TCR* gene rearrangement
- Aggressive clinical course

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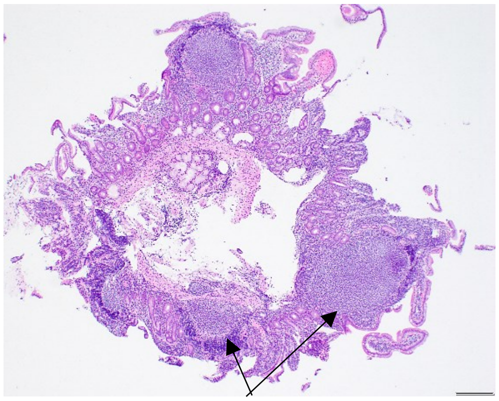
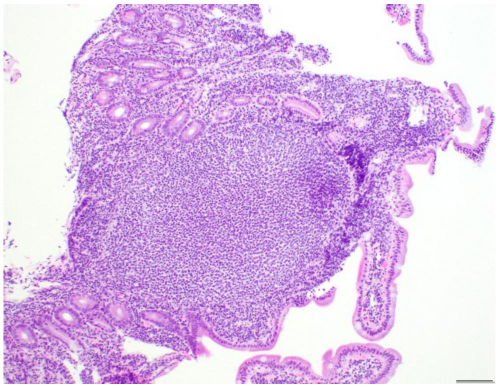


Many lymphoid aggregates



Neoplastic follicles lack tangible body macrophages and mantle zones

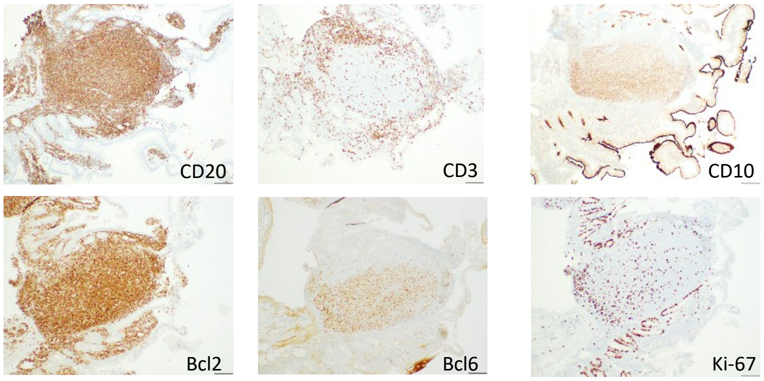
FOLLICULAR LYMPHOMA, DUODENAL TYPE

MORPHOLOGY

- **Lymphoma confined to the mucosa and/or submucosa of the duodenum**
- Almost always low grade (grade 1-2) unlike systemic follicular lymphoma; lamina propria is also infiltrated
- Neoplastic follicles lack tingible body macrophages and mantle zones
- IHC: CD20+, CD10+, BCL2+, low Ki-67

OTHER HIGH YIELD POINTS

- Lymphoma derived from follicular B lymphocytes
- Usually affects the second part of the duodenum but may involve jejunum and ileum; no systemic involvement
- **t (14;18)**
- **Excellent prognosis, local treatment, and indolent course**
- A small percentage of patients progress to nodal disease (<10%)



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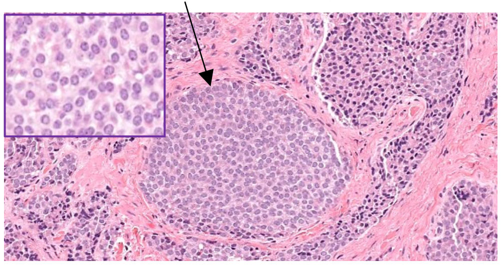
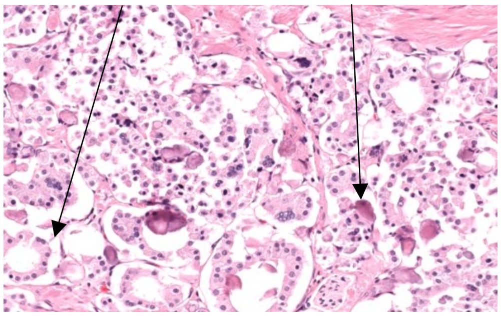
Nested architecture of NET with stippled chromatin

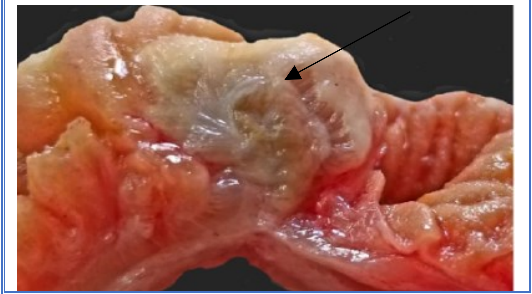


Psuedoglandular architecture

Somatostatinoma

Psammoma bodies





WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR

MORPHOLOGY

- Monotonous tumor cells with round/oval nuclei and **stippled (salt and pepper) chromatin**
- Architecture can be trabecular, nested, corded, ribbons, acinar, and/or pseudoglandular
- IHC: AE1/3+, Cam5.2+, Chromogranin-A+, Synaptophysin+, CK7-, CK20-

GRADING

Grade	Mitoses	Ki-67
1	<2 mitoses/2 mm^2	<3%
2	2-20 mitoses/2 mm^2	3-20%
3	>20 mitoses/2 mm^2	>20%

OTHER HIGH YIELD POINTS

- Majority of tumors are non-functioning; functional ones include
- **Gastrinoma:** Gastrin expressing NET in the duodenum; **causes Zollinger Ellison syndrome (**hypergastrinemia, peptic ulcer disease, diarrhea)
- **Somatostatinoma:** Somatostatin expressing NET in the ampulla; causes diabetes, stones, diarrhea; **psammoma bodies** is a characteristic feature
- **Carcinoid syndrome:** Diarrhea, bronchospasms, flushing, tricuspid valve fibrosis; occurs when liver metastasis present
- May be associated with syndromic conditions: **Multiple Endocrine Neoplasia (MEN) type 1** is associated with duodenal gastrinomas; ampullary somatostatinoma can arise in the setting of **Neurofibromatosis 1**
- Differential diagnosis: Poorly differentiated neuroendocrine carcinoma- large cell or small cell carcinoma; these lose well-differentiated NET architecture and cytology; instead, they have necrosis and prominent mitoses

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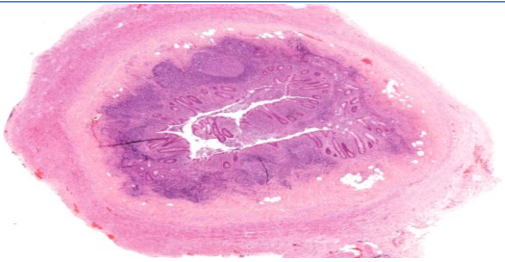
Gross image courtesy of Dr. José G. Bellassai, @BellassaiJb, used with permission

APPENDIX: NON-NEOPLASTIC



NORMAL HISTOLOGY

- Colonic-type epithelium with irregular glands/crypts and lamina propria
- **Prominent lymphoid aggregates in the mucosa/submucosa**
- Muscularis mucosae and submucosa may be attenuated but usually present
- Muscularis propria with longitudinal and circular smooth muscle

OTHER HIGH YIELD POINTS

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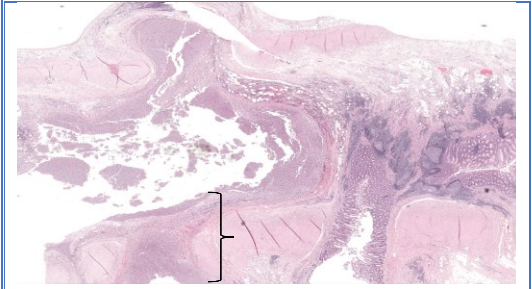
- Located in the retrocecal region commonly
- May have an immunological role



Transmural acute neutrophilic inflammation

ACUTE APPENDICITIS

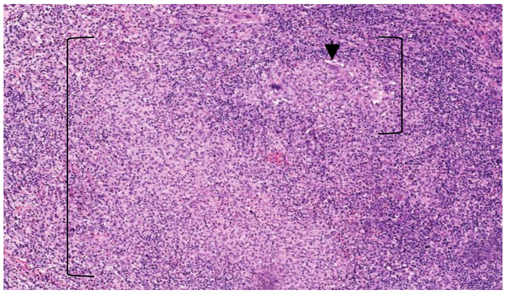
Path Presenter

MORPHOLOGY

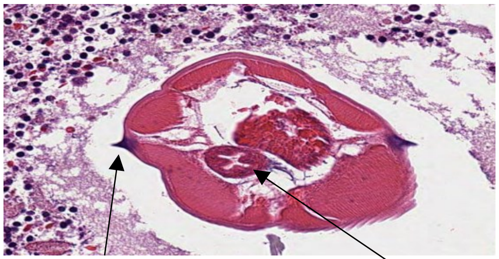
- **Neutrophilic infiltration** involving some or all layers
- Can be described as acute focal, suppurative, gangrenous, and perforated; can be associated with periappendicitis

OTHER HIGH YIELD POINTS

- Disease of the **young/adolescents** most commonly; Males > Females
- Pathogenesis: **obstruction** due to fecalith, lesions, hypertrophic lymphoid aggregates, diverticulosis, and/or vascular compromise leading to infection
- **Most common emergency abdominal surgery**



Granulomatous inflammation with a collection of histiocytes including giant cells(arrowhead)



Characteristic lateral ala (wing) Intestine

GRANULOMATOUS APPENDICITIS

MORPHOLOGY

- **Granulomatous or xanthogranulomatous inflammation** in addition to neutrophilic inflammation

OTHER HIGH YIELD POINTS

- Clinically resembles acute appendicitis
- Rare; seen in less than 2% of appendectomies
- Etiologies: **Idiopathic, *Yersinia*, interval appendicitis, *Mycobacterium tuberculosis* infection, pinworm (*Enterobius vermicularis*), sarcoidosis, Crohn disease**

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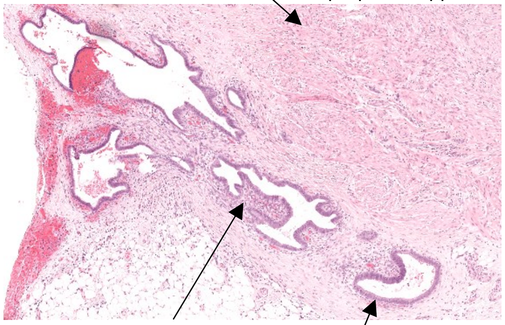
ENTEROBIUS VERMICULARIS/PINWORM:

- Granulomatous inflammation + **nematode with characteristic lateral alae**
- Pinworm is common in children and presents with **pruritis ani** (nocturnal pruritis) as female migrates to the anus and lays eggs
- Transmission occurs via the fecal-oral route and inhalation of dust-containing eggs
- Humans are the only natural host

Muscularis propria of appendix



Benign endometrial stroma Benign endometrial gland

ENDOMETRIOSIS

MORPHOLOGY

- **Ectopic benign endometrial glandular and stromal tissue**
- Sometimes stroma can be difficult to identify; in place, macrophages and hemosiderin pigment may be present (evidence of chronic hemorrhage)
- If cytologic atypia is present, atypical endometriosis is a consideration
- IHC: **CD10** highlights the stroma; glands are ER and PR positive

OTHER HIGH YIELD POINTS

- Appendix is an uncommon site; more common sites are ovary, fallopian tubes, cul de sac, and broad ligaments

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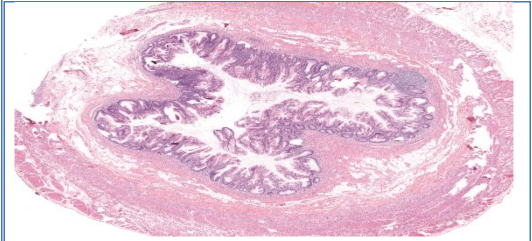
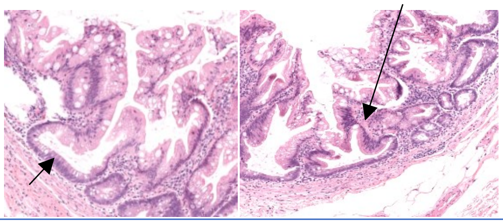
APPENDIX: NEOPLASTIC



Serrated lesion: L-shaped crypt T-shaped crypt



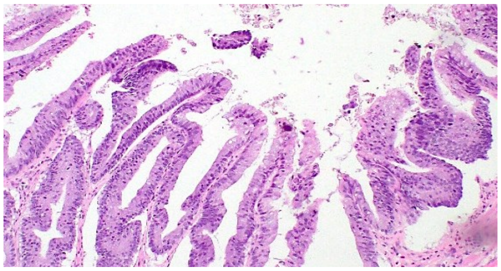
Appendiceal serrated lesions and polyps
Appendiceal neuroendocrine neoplasms
Appendiceal mucinous neoplasms
Appendiceal adenocarcinoma
Appendiceal goblet cell adenocarcinoma

SERRATED LESIONS AND POLYPS

MORPHOLOGY

- Mucosal epithelial polyps with serrations (saw-tooth) architecture
- **Hyperplastic polyp:** Luminal part shows serrations, bland cytology (no dysplasia) and the base is non-dilated
- **Serrated lesion without dysplasia:** The abnormal serrations extend to the crypt base with abnormal shapes (L-shaped, inverted T) and unequivocal basal dilatation; epithelium shows no dysplasia
- **Serrated lesion with dysplasia**: Epithelial atypia is also present and can be adenoma-like, serrated, or traditional serrated adenoma-like

Serrated lesion with low-grade serrated-type dysplasia



- Tubular adenoma/tubulovillous adenoma/villous adenoma and traditional serrated adenoma (rarely) can also occur in the appendix (see Colon section for details)

OTHER HIGH YIELD POINTS

- Males = females
- Hyperplastic polyps are usually seen in post-inflammatory conditions
- Serrated polyps have more *KRAS* than *BRAF* mutations

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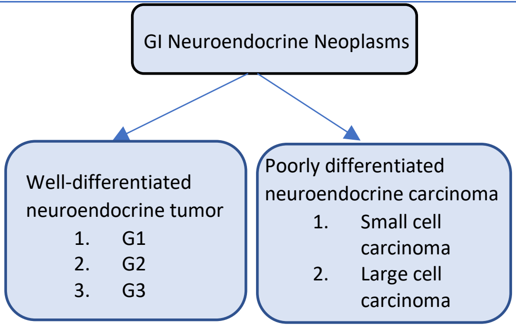
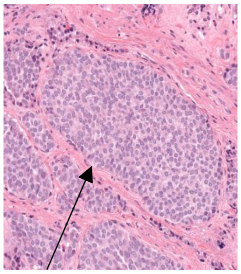
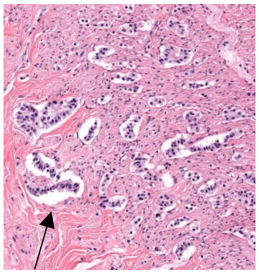

GI Neuroendocrine Neoplasms
Well-differentiated neuroendocrine tumor
1. G1
2. G2
3. G3
Poorly differentiated neuroendocrine carcinoma
1. Small cell carcinoma
2. Large cell carcinoma

EC-NET





Tubular NET

APPENDICEAL NEUROENDOCRINE TUMORS (NETs)

MORPHOLOGY

- Neuroendocrine tumors of the appendix are morphologically similar to other areas in the GI tract
- Enterochromaffin (EC)-cell NETs most common: polygonal monotonous tumor cells arranged in large nests with peripheral palisading
- L-cell NETs have a distinct trabecular or glandular growth pattern
- Tubular NET has stromal retraction and mimics adenocarcinoma
- Poorly differentiated neuroendocrine carcinoma of the appendix is extremely rare but morphologically like other organs
- IHC: Chromogranin-A and synaptophysin positive; EC-NET positive for serotonin
- For grading, please see the small bowel section

OTHER HIGH YIELD POINTS

- **Most common appendiceal tumor** by far
- Found incidentally or with acute appendicitis
- NETs mainly occur at the tip
- Slight female predominance and majority <40 years
- **Good prognosis (>95%)** if confined to the appendix

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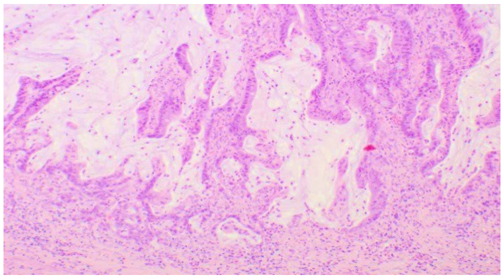
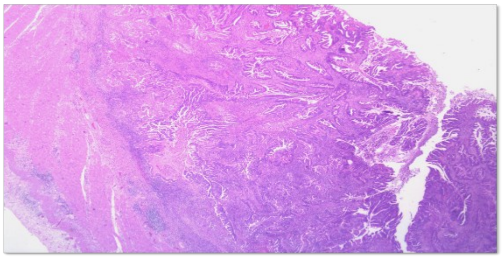
Mucinous adenocarcinoma





Non-mucinous adenocarcinoma

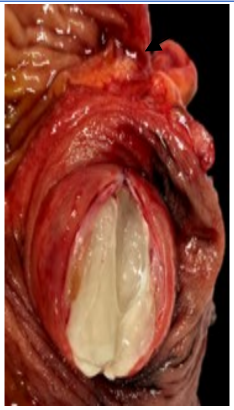
APPENDICEAL ADENOCARCINOMA

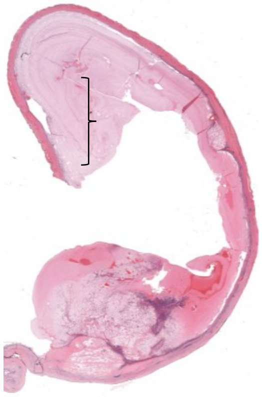
MORPHOLOGY

- Malignant glandular neoplasm with infiltrative edges and morphology similar to that seen in colon cancer
- **Mucinous adenocarcinoma:** Extracellular mucin comprising >50% of tumor with floating strips/glands/clusters of malignant epithelial cells
- **Non-mucinous adenocarcinoma:** Irregular glands infiltrating the wall of the appendix with desmoplastic stroma
- **Signet-ring cell carcinoma:** >50% of tumor composed of signet-ring cells which may sometimes be in pools of mucin
- **Undifferentiated carcinoma:** Rare

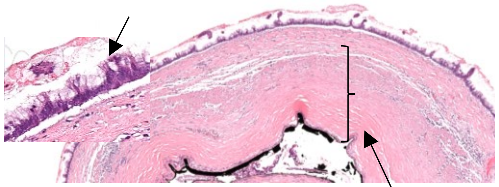
OTHER HIGH YIELD POINTS

- 5-6th decade; can occur anywhere in the appendix
- Presentation can be of appendicitis, abdominal pain, mass, GI bleed, and/or obstruction
- *KRAS* and *GNAS* mutations in mucinous carcinomas; microsatellite instability in non-mucinous adenocarcinomas
- Patients with mucinous carcinoma have a better outcome than ones with non-mucinous carcinoma
- Differential diagnosis: LAMN (LAMN lacks infiltrating invasion)

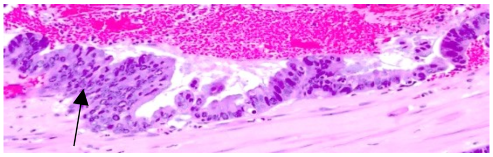




Low-grade epithelium



Lamina propria/submucosa replaced by fibrosis



High-grade appendiceal mucinous neoplasm

APPENDICEAL MUCINOUS LESIONS

- Low-grade Mucinous Neoplasm (LAMN)
- High-grade Mucinous Neoplasm (HAMN)

MORPHOLOGY

- LAMN has **hypermucinous epithelium** with villous/serrated architecture, low-grade columnar to cuboidal epithelium resembling **low-grade dysplasia**
- Has broad borders with **pushing-type invasion with fibrosis** of lamina propria and submucosa, and very attenuated to non-existent submucosal lymphoid aggregates
- Mucin may dissect through the wall of the appendix (with or without epithelium) and disseminate into the peritoneum (pseudomyxoma peritonei)
- HAMNs are rare; **high-grade cytology**, complex architecture with similar growth pattern as LAMN (such as pushing borders, subepithelial fibrosis, pushing invasion, rupture)

OTHER HIGH YIELD POINTS

- Males = females; wide-age range with most common in the sixth decade
- LAMN shows ***KRAS* and *GNAS*** mutations; higher grade tumors less commonly have *GNAS* mutations; *GNAS* mutation associated with mucin production
- Prognosis depends on stage with great prognosis in tumors limited to the appendix and variable prognosis if peritoneal dissemination present
- Hyperthermic intraperitoneal chemotherapy with cytoreduction has increased survival
- Differential diagnosis: Diverticula can rupture and extrude mucin and mimic LAMN

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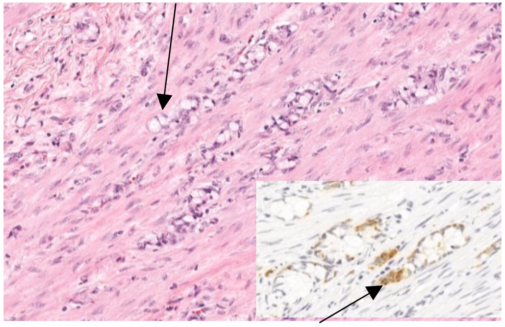
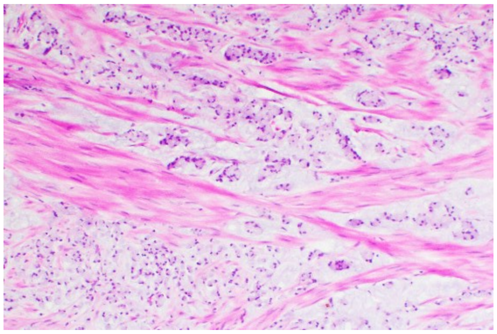
Grade 1 Clusters of goblet-like cells and endocrine cells



Synaptophysin highlighting neuroendocrine cells



Grade 3 (<50% tubular/clustered pattern)

APPENDICEAL GOBLET CELL ADENOCARCINOMA (GCA)

MORPHOLOGY

- **Amphicrine (having both endocrine and exocrine features) tumor with goblet-like mucinous cells, endocrine cells, and Paneth-like cells**
- Low-grade pattern: Tubules and clusters of goblet-like mucinous cells; endocrine and Paneth-like cells with granular eosinophilic cytoplasm, mild nuclear atypia, and no stromal reaction
- High-grade pattern: Tumor cells infiltrating as single cells, complex anastomosing tubules, cribriform masses, or sheets, signet-ring cells (areas of classic low-grade morphology are still present even if focally)
- IHC: Chromogranin-A and synaptophysin highlight variable cells; not required

TUMOR GRADING

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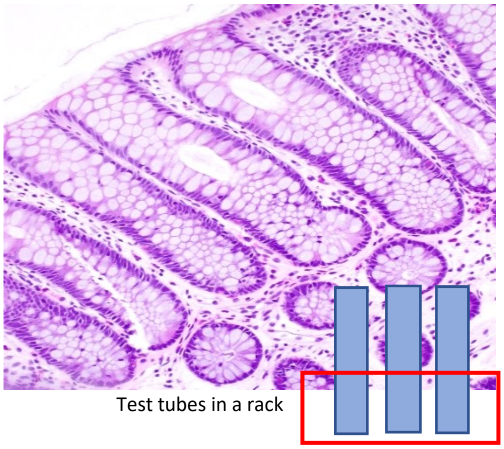
Grade	Tubular/Clustered (Low-grade Pattern)	High-grade pattern
G1	>75%	<25%
G2	50-75%	25-50%
G3	<50%	>50%

OTHER HIGH YIELD POINTS

- Previously known as "**Goblet cell carcinoid" or "Adenocarcinoma ex Goblet cell carcinoid**
- Often involves distal appendix; males= females; mean age: 50-60 years
- Usual affects the distal appendix
- Mutations in the **WNT signaling pathway (***CTNNA1, CTNNB1*) and chromatin remodeling genes (*ARID1, ARID2*); ***TP53*** mutations in high-grade tumor

COLON: NORMAL



MORPHOLOGY

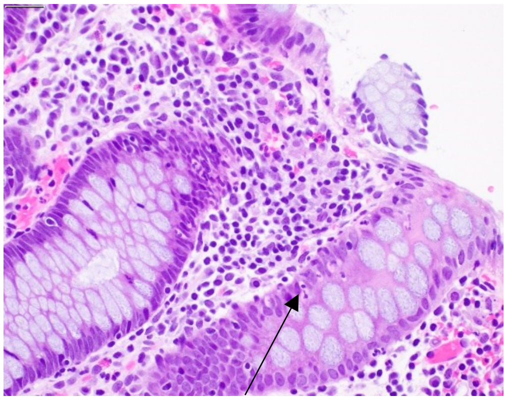
- In the colonic mucosa, crypts should be oriented parallel to one another, perpendicular to the surface (like test tubes in a rack), resting on the muscularis mucosae
- Muciphages in the rectum are considered normal
- Colon layers: Mucosa, submucosa, muscularis propria, subserosa, and serosa

OTHER HIGH YIELD POINTS

REGIONAL VARIATION	
Right colon	**Left colon**
More lymphocytes	Less lymphocytes
Paneth cells normal	Paneth cells abnormal
Fewer goblet cells	More goblet cells

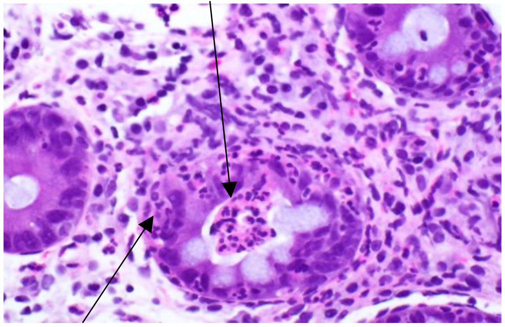
INFLAMMATORY/NON-NEOPLASTIC CONDITIONS OF THE COLORECTUM

- Focal active colitis
- Acute colitis
- Chronic active colitis
- Ischemic colitis
- Pseudomembranous colitis
- Eosinophilic colitis
- Graft Versus Host Disease
- Microscopic colitis: lymphocytic and collagenous
- Granulomatous colitis
- Mucosal prolapse/solitary rectal ulcer syndrome
- Pigments and inorganic material
- Radiation colitis/proctitis
- Diverticular disease



Focal active colitis: Rare neutrophils in crypts

Crypt abscess (neutrophils in the lumen of the gland)



Cryptitis

FOCAL ACTIVE COLITIS

MORPHOLOGY

- Terminology used when **rare collections of neutrophils** are identified in crypt epithelium (otherwise normal)

OTHER HIGH YIELD POINTS

- **Etiology:** Bowel preparation artifact (most commonly); other etiologies are medications (especially NSAIDs), acute self-limited colitis (resolves in <4 weeks; commonly implicated organisms are *Campylobacter, Salmonella, Shigella* or *Yersinia*; with abrupt onset of fever), ischemic colitis, and inflammatory bowel disease (more insidious onset)

ACUTE COLITIS

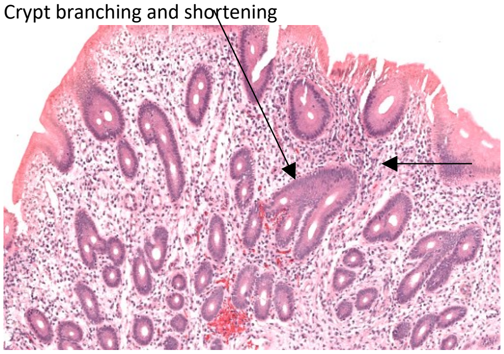
MORPHOLOGY

- Terminology used when there is **easily visible cryptitis (neutrophils in the crypts) and crypt abscesses, WITHOUT features of chronicity**

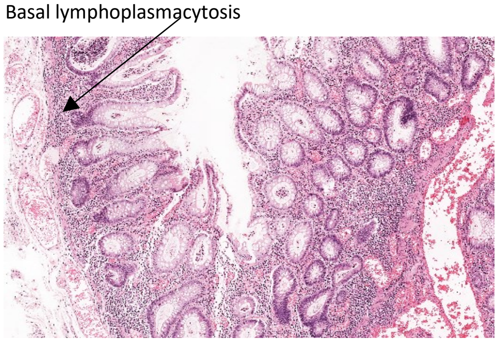
OTHER HIGH YIELD POINTS

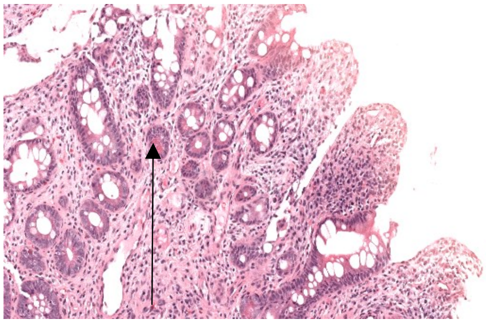
- **Etiology considerations:**
  - **Infections:** Usually acute bacterial or viral infections (e.g. *Cytomegalovirus, Salmonella, Shigella, Campylobacter, Yersinia, Aeromonas, Clostridium Difficile, E.coli*), so make sure this has been evaluated clinically; often food contamination (fecal-oral); may see pseudomembranes
  - **Medications:** Especially NSAIDS; others include Kayexalate, Sevelamer, Ipilimumab (immune checkpoint inhibitors)
  - **Inflammatory bowel disease:** Usually has features of chronicity; however, emerging or partially treated cases can show acute colitis only

Crypt branching and shortening



Basal lymphoplasmacytosis





Paneth cell metaplasia

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CHRONIC ACTIVE COLITIS

MORPHOLOGY

- Acute inflammation, cryptitis, crypt abscesses, ulcers/erosions and

FEATURES OF CHRONICITY
Architectural distortion (crypt branching, loss, and shortening)
Basal lymphoplasmacytosis
Paneth cell or pyloric gland metaplasia

OTHER HIGH YIELD POINTS

ETIOLOGIES

- **Inflammatory bowel disease (IBD):** Chronic systemic autoimmune inflammatory disease; on a mucosal biopsy, it can be impossible to distinguish Crohn from Ulcerative colitis; the purpose of biopsies is to assess activity and dysplasia
- **Infection**: Always rule out cytomegalovirus in refractory inflammatory bowel disease
- **Diverticular disease:** Most common in older patients in sigmoid colon; can mimic IBD with diverticulitis and Segmental Colitis Associated with Diverticulosis (SCAD)
- **Diversion-associated colitis**: In bowel diverted from fecal stream (causes short chain fatty acid deficiency); microscopic finding is **florid lymphoid hyperplasia with prominent germinal centers**
- **Sexually Transmitted Diseases (STD) proctocolitis**: Usually biopsies show abundant plasma cells; common culprits- *Syphilis* and *Chlamydia* (lymphogranuloma venereum)
- **Cord Colitis Syndrome:** Chronic active colitis feature with granulomas; seen in the setting of umbilical cord transplantation
- **Medications:** NSAIDs, Ipilimumab, resins.

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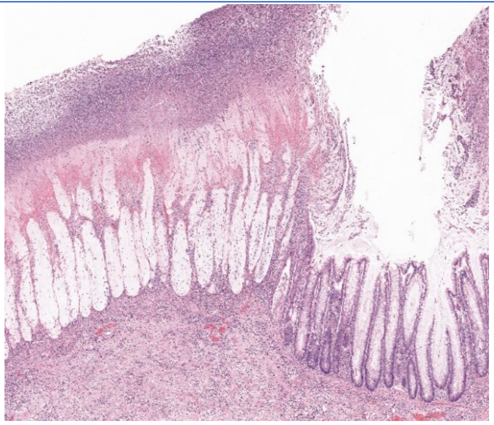

Mushroom-like exudate with neutrohils, mucin, and debris

PSEUDOMEMBRANOUS COLITIS

MORPHOLOGY

- **Acute colitis with adherent inflammatory exudate (pseudomembrane)** overlying sites of mucosal injury
- Crypts show superficial necrosis and dilatation; later crypts can be necrotic and mimic ischemic colitis
- **Pseudomembranes:** Mucopurulent exudate erupts out of crypts in a mushroom-like cloud with debris, neutrophils, and extracellular mucin

OTHER HIGH YIELD POINTS

- **Usually occurs after broad-spectrum antibiotics**
- 25% caused by *Clostridium difficile*; other organisms include *Clostridium perfringens, Staphylococcus, Klebsiella oxytoca, Candida, Salmonella*
- Differential diagnosis: **Ischemia and other infections** (such as *E. coli*)

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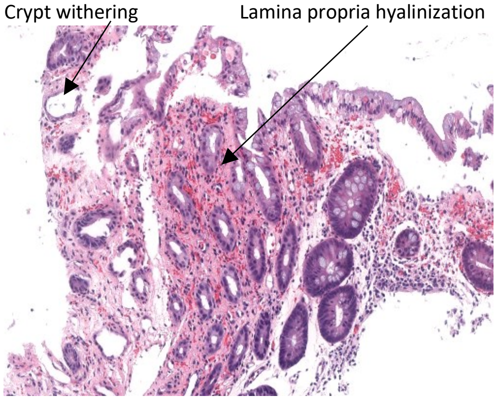

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ISCHEMIC COLITIS

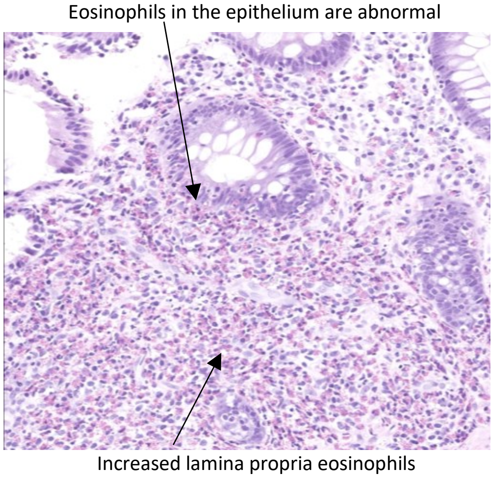
MORPHOLOGY

- Superficial epithelial damage, crypt withering, lamina propria hyalinization and hemorrhage, and mild acute inflammation; Deeper crypts near the muscularis mucosae may appear more viable with reactive changes

OTHER HIGH YIELD POINTS

ETIOLOGIES

- **Ischemia:** Due to poor perfusion; **most common in "watershed" areas** (splenic flexure, rectosigmoid, and ileocecal regions) in older patients with vascular occlusion or low-flow states
- **Infections:**
  - ***E. coli* O157:H7 (EHEC)-** Endothelial damage from toxin→ fibrin thrombi often seen; associated with Hemolytic Uremic Syndrome (anemia, low platelets, renal failure)
  - ***C. Difficile***- Pseudomembranes, less hyalinization and crypt withering
- **Medications:** NSAIDs, kayexalate, sevelamer, ipilimumab


Eosinophils in the epithelium are abnormal
Increased lamina propria eosinophils

EOSINOPHILIC COLITIS

MORPHOLOGY

- Increased intraepithelial and lamina propria eosinophils; any in the submucosa or muscle are abnormal
- No strict cut-off, **>60 eosinophils is likely too many**

OTHER HIGH YIELD POINTS

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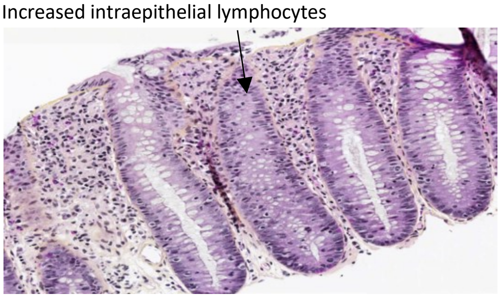
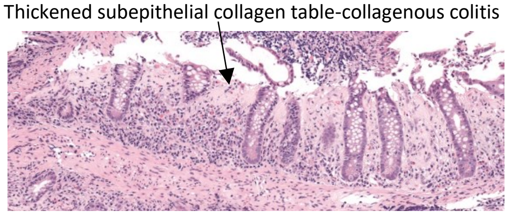
ETIOLOGIES

- Parasites
- Connective tissue disease/vasculitis
- Food allergies
- Medications
- Systemic mastocytosis
- Inflammatory bowel disease (particularly Crohn)
- Eosinophilic colitis/gastroenteritis: Diagnosis of exclusion; can be associated with eosinophil-rich inflammation in other organs (e.g., esophagus and/or small bowel); layer of bowel involved determines symptoms





MICROSCOPIC COLITIS

- **Chronic watery non-bloody diarrhea**; **normal endoscopic** findings
- Etiologies: Idiopathic, viral infections, medications (NSAIDs, Olmesartan, antidepressants)

MORPHOLOGY

- **Lymphocytic colitis:** Increased intraepithelial lymphocytes (>20 lymphocytes/100 epithelial cells) and surface epithelial damage
- **Collagenous colitis:** Increased subepithelial collagen layer (irregular thickening, trapped inflammatory cells, blood vessels, and fibroblasts) and increased intraepithelial lymphocytes; trichrome stain highlights the collagen layer

OTHER HIGH YIELD POINTS

- Classically affects the **right colon** more than left; **females > males**
- Mild cases can be treated with loperamide, mesalazine, bismuth while moderate to severe cases with steroids

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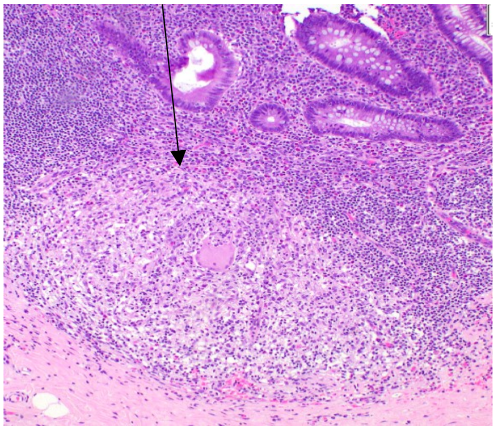
Granulomatous inflammation



GRANULOMATOUS COLITIS

MORPHOLOGY

- **Granulomas are collections of histiocytes with surrounding lymphocytic cuff**; they can be necrotizing, non-necrotizing, well-formed, ill-defined (vague)
- **Granulomatous** inflammation warrants **AFB/FITE and GMS/PAS-D** stains to rule out infectious etiologies

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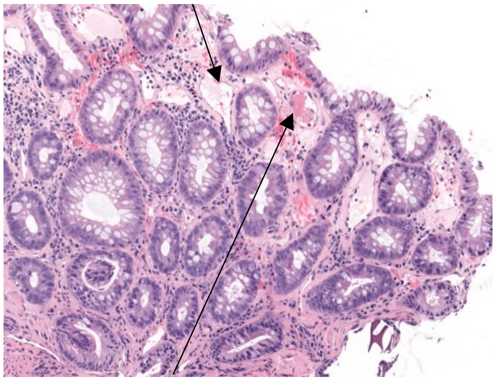
OTHER HIGH YIELD POINTS

ETIOLOGIES

- **Crohn disease:** Loose, non-necrotizing granulomas; seen in less than half of the cases; of note, ulcerative colitis can have granulomatous reaction to crypt rupture
- **Infections:** Especially if necrotizing, rule out fungi and mycobacteria; look for parasites (such as schistosomiasis); *Yersinia*
- **Sarcoidosis:** Well-formed epithelioid granulomas that sometime coalesce
- **Other etiologies:** Medications, cord-colitis syndrome, diverticular disease, common variable immunodeficiency, non-specific mucosal injury

Dilated mucosal vessels



Fibrinoid vascular necrosis

RADIATION COLITIS/PROCTITIS

MORPHOLOGY

- Acute changes (1-2 months): **Lamina propria edema**, **fibrinoid vascular necrosis,** ulcer, epithelial atypia, increased epithelial apoptoses, mucosal neutrophil inflammation with **increased eosinophils**
- Late changes (months or years later): mucosal atrophy with crypt loss, fibrosis, **dilated telangiectatic vessels and vessel hyalinization and intimal thickening**; may see crypt architectural distortion, Paneth cell metaplasia, and fibrosis

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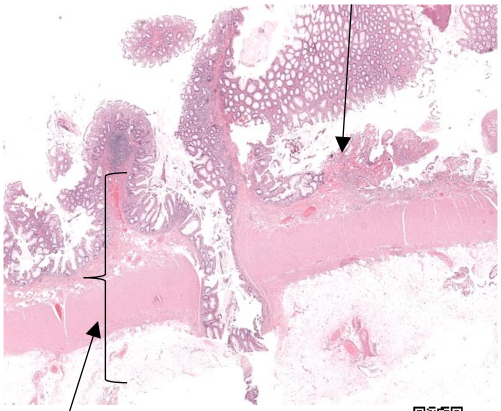
OTHER HIGH YIELD POINTS

- History of radiation to pelvic or abdominal malignancy
- **Rectosigmoid** is most commonly affected
- Symptoms can be within 1-2 months of therapy or months or years later
- Differential diagnosis: Ischemia, IBD

Segmental colitis associated with diverticulosis (SCAD)



Diverticulum

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DIVERTICULAR DISEASE

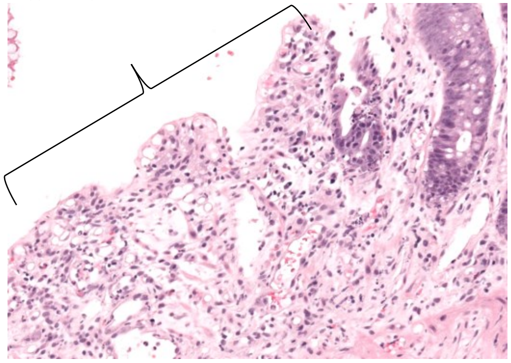
MORPHOLOGY

- **Outpouching of colonic mucosa** and submucosa through the muscularis propria covered by subserosa/serosa (most are false diverticula); true diverticula are uncommon and involve outpouching of all layers of the intestinal wall
- Diverticulosis can be **complicated by acute/chronic diverticulitis** (4-15%), hemorrhage, and segmental colitis associated with diverticulosis (SCAD)

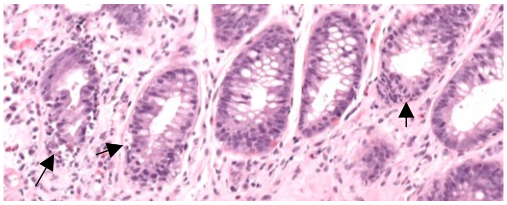
OTHER HIGH YIELD POINTS

- **Sigmoid and descending colon are the most common sites**; right-sided diverticular disease more common in Asia
- Highest incidence in the western world; prevalence increases with age
- Etiology: Abnormal colonic motility leads to increased segmental contractions, increased intraluminal pressure, and diverticula formation
- SCAD can mimic IBD; however, changes are limited to vicinity of diverticula

Crypt drop-out/loss



Crypt epithelial apoptoses



GRAFT VERSUS HOST DISEASE (GVHD)

MORPHOLOGY

- **Complication of stem cell transplantation**
- Characteristic features are **crypt apoptosis**, crypt dropout, and ulceration
- Inflammation tends to be sparse
- Architectural distortion and fibrosis are markers of long-standing rejection

LERNER SYSTEM FOR GRADING GVHD

Grade	Findings
1	Isolated apoptotic bodies
2	Loss or damage of isolated crypts, w/ or w/o crypt abscesses
3	Loss of two or more contiguous crypts
4	Extensive crypt loss with epithelial destruction

OTHER HIGH YIELD POINTS

- Donor T-cells recognize host tissue antigens as foreign leading to T-cell activation→ cytokine storm→ end organ damage
- **Skin > gastrointestinal tract > liver** affected

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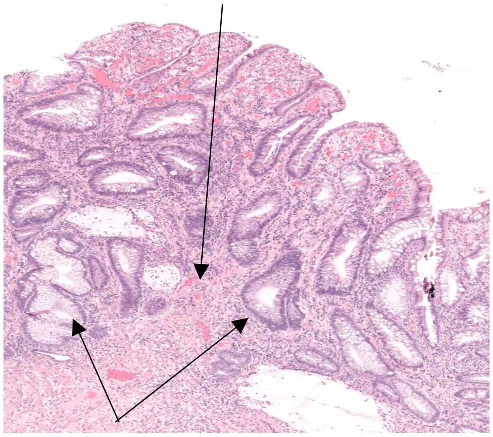
Muscle fibers splaying into the lamina propria



Distortion of crypts

SOLITARY RECTAL ULCER SYNDROME/MUCOSAL PROLAPSE

MORPHOLOGY

- Prolapse features **include thickened muscularis mucosae fibers with splayed fibers extending into the lamina propria**
- Other features include superficial mucosal ulceration, villiform change, crypt hyperplasia and distortion, ectatic vessels
- Late changes may mimic colitis cystica profunda

OTHER HIGH YIELD POINTS

- Solitary or multiple ulcerated or polypoid lesions, 4-10 cm from anal margin
- 3-4th decade; more common in women
- Etiology: **abnormal function of anal/pelvic floor muscles during defecation**

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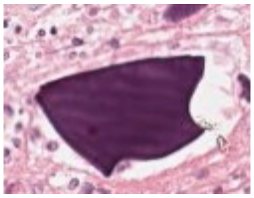
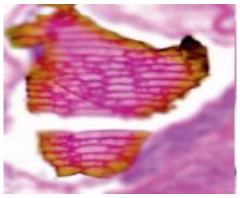
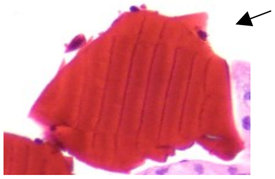
Kayexalate: Purple+fish scales



Sevelamer: Pink to yellow





Cholestyramine: Bright pink to orange

Image courtesy of Dr. Monika Vyas Twitter @Mvgs1706, used with permission

PIGMENTS AND INORGANIC MATERIAL

MEDICATION RESINS

- **Kayexalate: Used to treat hyperkalemia** in renal failure; it causes ischemic and ulcerative changes; linked to fatalities, so can be a critical diagnosis; **Purple** on H&E with narrow **fish-scale** pattern
- **Sevelamer: Used to treat hyperphosphatemia** in renal failure; can be associated with mucosal injury; **bright pink to rusty yellow** on H&E with an irregular fish-scale pattern
- **Bile acid sequestrants (cholestyramine):** Binds bile acids (lowers cholesterol); not associated with injury; bright pink to orange on H&E with classically smooth, glassy texture (scales may be present as an artifact of knife cutting)

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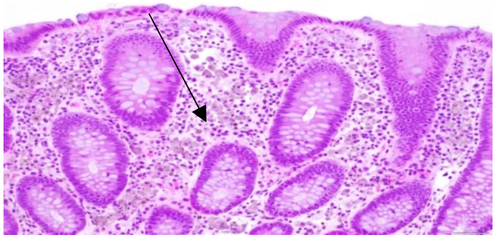
Brown pigment-laden macrophages in lamina propria



MELANOSIS COLI

- **Fine brown-black pigment in the cytoplasm of macrophages** commonly found in the lamina propria
- **Consists of lipofuscin**; although classically associated with **laxative use**, it can be seen with any other disorder with increased epithelial turnover, including constipation
- Differential diagnosis: Hemosiderosis (pigment is bright-brown and coarse)- iron stain positive

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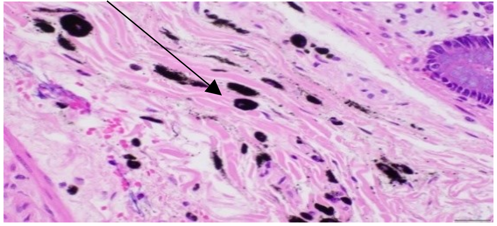
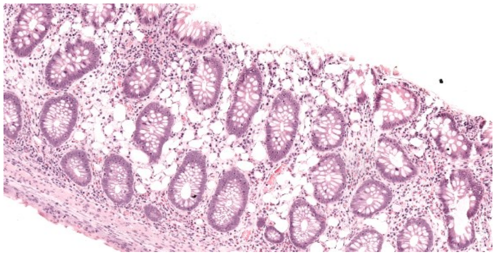
Tattoo pigment



TATTOO PIGMENT

- **Black coarse granules in macrophages** often with foreign-body giant cell reaction
- Used to **mark lesions endoscopically for later identification**

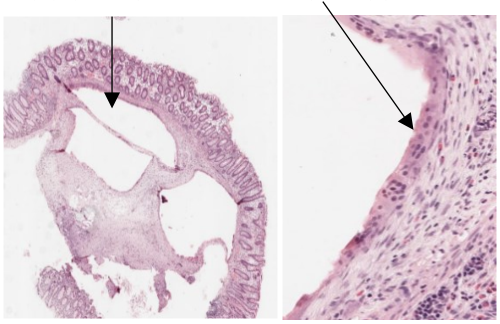


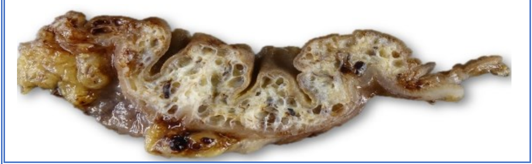
Pseudolipomatosis

PSEUDOLIPOMATOSIS/AIR

- Empty spaces without associated foreign body giant cell reaction seen in colorectal biopsies commonly
- **Attributed to insufflation artifact;** no associated nuclei; tend to be variable in size
- Differential diagnosis: Mucosal lipoma (associated with Cowden syndrome)
- IHC: S100 negative

Empty spaces (gas-filled) with foreign body giant cells





PNEUMATOSIS CYSTOIDES INTESTINALIS

- **Empty spaces (gas-filled) with foreign body giant cell reaction** (the reaction implies it happened in vivo)
- May occur in children and adults
- Can be incidental or associated with severe disease
- In adults, can be idiopathic or due to infection with gas-producing bacteria such as *Clostridia,* drugs, chemotherapy, obstruction, pulmonary disease or connective tissue disease

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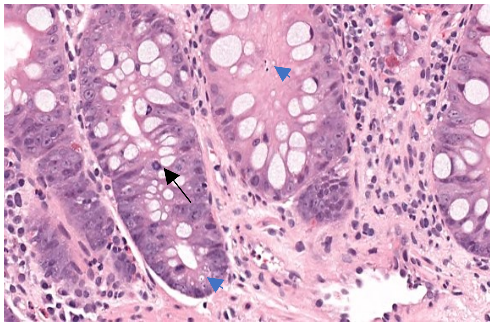
Gross image courtesy of Dr. Brian Cox @Dr_Brian_Cox, used with permission

MEDICATION INDUCED INJURY

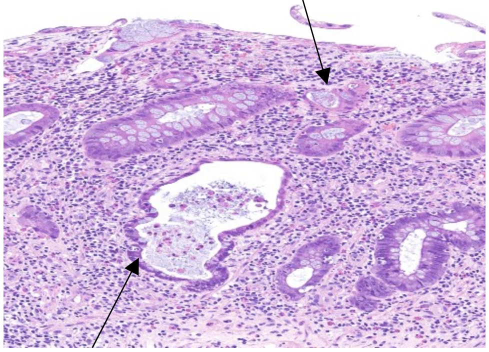
Pattern of colitis	Associated drug
Eosinophilic colitis	NSAIDs, gold, carbamazepine, antiplatelet agents, estrogens
Lymphocytic or collagenous colitis	NSAIDs, lansoprazole, ticlopidine, ranitidine, simvastatin, flutamide, carbamazepine, sertraline, penicillin, checkpoint inhibitors, Idelalisib
Focal active colitis	NSAIDs, Bowel preparation (esp. oral sodium phosphate), checkpoint inhibitors, Idelalisib
Ischemic colitis	NSAIDs, antibiotics, amphetamines, digitalis, diuretics, chemotherapy, nasal decongestants, constipation-inducing medications, laxatives, vasopressor agents, cocaine, ergotamine, serotonin agonists/antagonists including sumatriptan,

	estrogen, progesterone, glutaraldehyde, and immunomodulators such as interleukin
Apoptotic colitis	Bowel preparation (esp. oral sodium phosphate), mycophenolate mofetil, laxatives, chemotherapeutic agents (esp. 5-fluorouracil), NSAIDs, cyclosporine, checkpoint inhibitors, Idelalisib, TNF-alpha inhibitors
Pseudomembranous colitis	NSAIDs, antibiotic-associated Clostridium difficile colitis
Neutropenic colitis	Chemotherapy
Mucosal ulcers, erosions, and strictures	NSAIDs, methotrexate, nonabsorbable drugs: Kayexalate, sevelamer, colesevelam



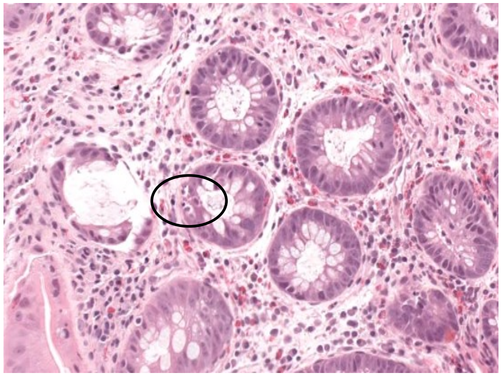
Ring mitosis (black arrow) Apoptoses (blue arrows)

Regenerative crypt with atypia after injury



Crypt drop-out with apoptoses

Mycophenolate mofetil injury: Apoptotic bodies



CHARACTERISTIC INJURY PATTERNS AND MEDICATIONS

CHOLCHICINE

- Multiple arrested metaphase mitoses, particularly "rings;" increased apoptotic bodies and reactive changes
- Used in the treatment of gout
- Inhibits microtubule polymerization→ interferes with mitosis, chemotaxis, and neutrophil degranulation

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CHEMOTHERAPY-RELATED INJURY

- Epithelial atypia, sometimes mimics dysplasia
- Taxol causes ring mitoses similar to colchicine
- Severe neutropenia can cause "neutropenic colitis" where after mucosal damage opportunistic bacteria invade and cause necrosis and pneumatosis leading often to septic shock

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MYCOPHENOLATE MOFETIL INJURY

- Immunosuppressive drug usually used after solid organ transplantation
- GI toxicity often limits the use
- Increased crypt apoptoses, patchy neutrophilic infiltration, degenerated damaged crypts, scattered eosinophils
- Differential diagnosis: Graft vs Host disease (less eosinophils)

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CHECKPOINT INHIBITOR INJURY

- Anti-PD1, anti PD-L1, and anti-CTLA therapies
- Activate immune tumor destruction, but can also cause autoimmune "immune-related adverse events"
- Responds to steroids
- Microscopic findings include all or some of the findings of lymphocytic colitis, collagenous colitis, acute self-limited colitis, and apoptotic colitis

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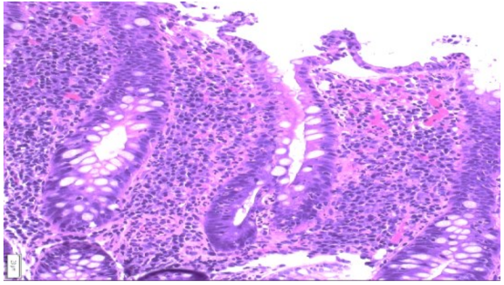
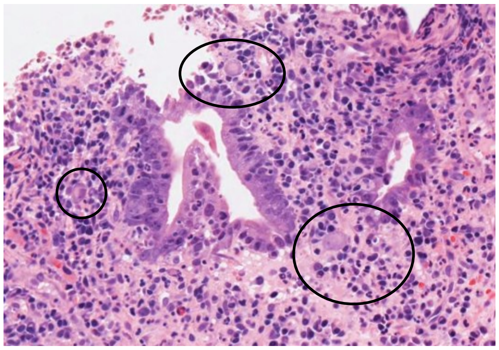


IDELALISIB

- Specific small molecule drug used to treat chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular lymphoma
- Causes severe diarrhea
- Overlapping injury morphology as with checkpoint inhibitors such as increased apoptoses, lymphocytic colitis, and active colitis

COLON: INFECTIOUS ETIOLOGIES


Viral inclusions in stromal cells (circled)

CYTOMEGALOVIRUS

MORPHOLOGY

- Cytomegaly with **nuclear "owl's eye (Cowdry-A) pink, nucleolus-like inclusions and cytoplasmic granular and pink to purple hof-like inclusions**
- Cells affected commonly are stromal and endothelial cells
- Background may show ulceration, mixed inflammation infiltrates rich in neutrophils; immunosuppressed patients may show less inflammation

OTHER HIGH YIELD POINTS

- Most common in **immunocompromised hosts** such as Human Immunodeficiency Virus (HIV) patients, inflammatory bowel disease patients on therapy, and graft versus host disease cases

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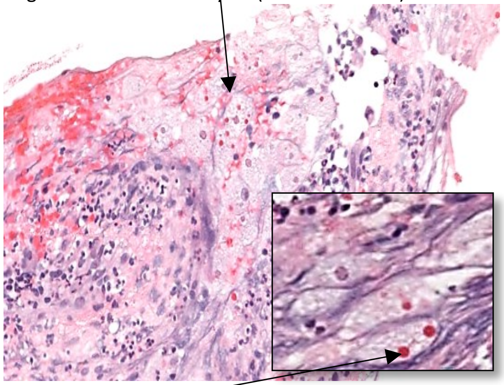

AMEBIASIS

MORPHOLOGY

- Infection caused by pathogenic species of amebae, mostly ***Entamoeba Histolytica***
- Amebae: trophozoites that are 10-60 µ, nucleus 3-5 µ with central condensation of chromatin and peripheral rim of chromatin; numerous fine vacuoles in the cytoplasm give them a **foamy appearance mimicking histiocytes; the clue is to look for ingested red blood cells**
- Discrete **ulcers (flask-shaped)** with intervening normal mucosa
- Stains: Negative for CD68 and positive for PAS and Trichrome

OTHER HIGH YIELD POINTS

- Commonly involves the colon, most commonly cecum and right colon
- Usually asymptomatic but may present as fulminant colitis

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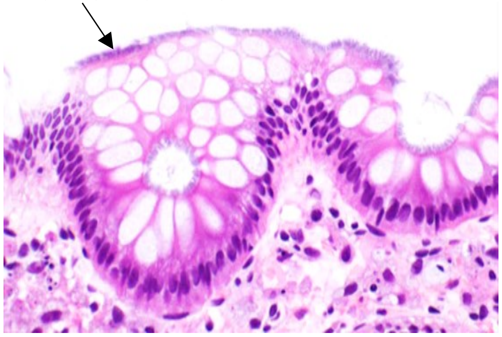
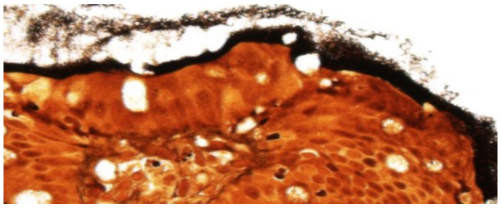


SPIROCHETOSIS

MORPHOLOGY

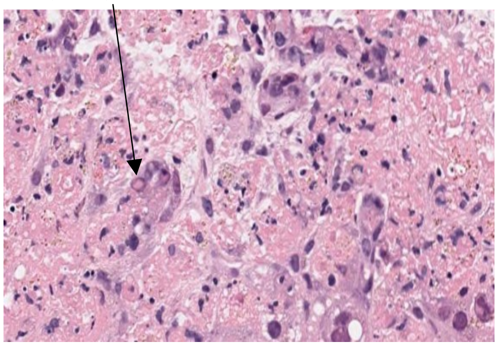
- **Fuzzy, fringed layer of organisms at the surface of epithelium** (non-invasive)
- No associated inflammatory infiltrate
- Stains: Positive for silver stains (Warthin-starry, Steiner) and spirochete immunohistochemical stain

OTHER HIGH YIELD POINTS



Warthin-starry stain- highlighting the spirochetes

Smudy basophilic inclusions of adenovirus



- Variable spirochete species, but most are ***Brachyspira aalborgi or Brachispira pilosicoli***
- More common in the developing world, HIV patients, and men
- Most cases are asymptomatic; if associated with diarrhea, can treat with antibiotics   Path Presenter

ADENOVIRUS

MORPHOLOGY

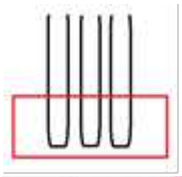
- **Smudgy basophilic inclusions** in the surface epithelium, often in goblet cells → can be round or crescent-shaped
- Colon shows increased apoptosis and epithelial sloughing

OTHER HIGH YIELD POINTS

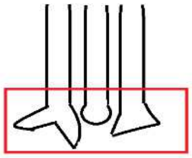
- **Common cause of childhood diarrhea**; can cause intussusception due to lymphoid hyperplasia
- In immunocompromised hosts, can cause diarrhea and potentially disseminated disease (hepatitis and pneumonitis) and death

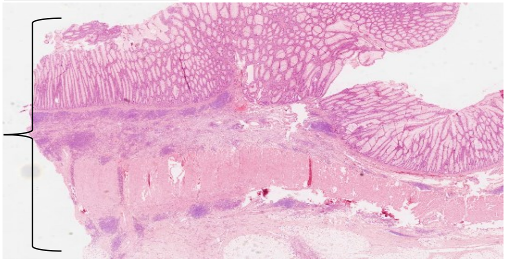
COLON: INFLAMMATORY BOWEL DISEASE

Normal colon

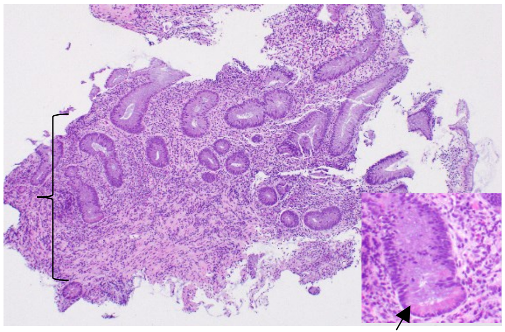


Architectural distortion





Transmural chronic inflammation in Crohn



Architectural distortion   Paneth cells

Nomenclature for colitis	Morphologic features
Acute	Neutrophils in the epithelium, glandular lumens
Chronic	Architectural distortion Basal lymphoplasmacytosis Paneth cell metaplasia (left colon) Pyloric metaplasia (mostly in small bowel)

CROHN DISEASE

MORPHOLOGY

- Patchy **transmural** chronic active inflammation involving upper and lower gastrointestinal tract
- Characteristic features are **transmural inflammation, skip lesions, granulomas, ulcers (superficial aphthous type to fissuring), muscle and nerve hypertrophy, pyloric gland metaplasia, fibrosis/strictures, and fistulas including perianal fistulas, pseudo-polyps, creeping fat**

OTHER HIGH YIELD POINTS

- Onset of disease at 20-40 years with a second peak in 50-60 years
- Small bowel involvement in 80%, ileocolonic involvement in 30-40%
- Extraintestinal manifestations: arthritis, uveitis, pyoderma gangrenosum, primary sclerosing cholangitis, and pulmonary processes
- Increased risk of dysplasia and carcinoma

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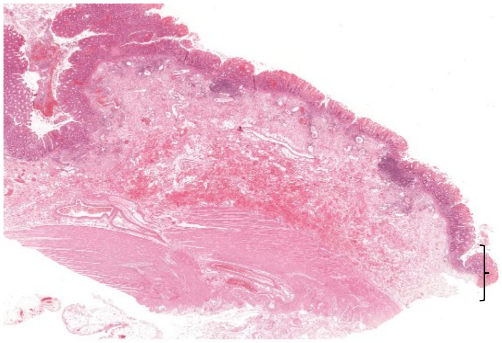
ULCERATIVE COLITIS

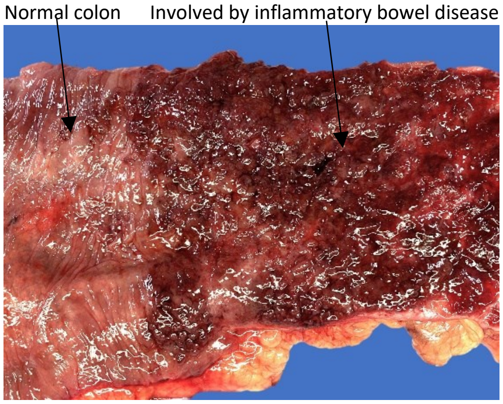
MORPHOLOGY

- Chronic active inflammation in **the rectum** proceeding proximally in a continuous **diffuse** pattern (pan-colitis)
- Changes are limited to the **mucosa and superficial submucosa** with ulceration

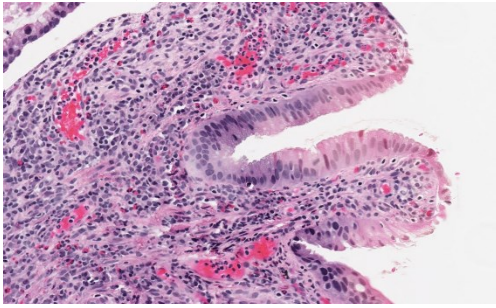
Ulcerative colitis: changes limited to mucosa



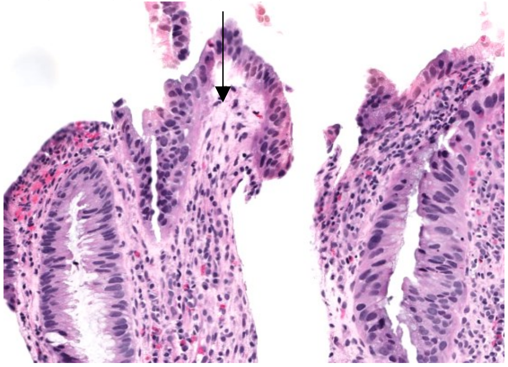
Normal colon Involved by inflammatory bowel disease



Indefinite for dysplasia (surface still shows maturation)



Low grade dysplasia: Atypical cells extend to the surface



- Small bowel usually not involved but can see mild inflammation in terminal ileum in 20% ("backwash ileitis"); absence of granulomas; no fistulas or fissures; toxic megacolon; pseudopolyps

OTHER HIGH YIELD POINTS

- Onset of disease at 15-30 years with a second peak in 50-70 years
- Extraintestinal manifestations similar to Crohn disease
- Increased risk of dysplasia and carcinoma

Path Presenter

INDETERMINATE COLITIS

- 10% of inflammatory bowel disease patients are unclassifiable, often due to pathologic and clinical overlap between Ulcerative colitis and Crohn disease

DYSPLASIA IN INFLAMMATORY BOWEL DISEASE

- Inflammation→ DNA oxidative damage→ Cancer
- Risk proportion to severity and duration of inflammation
- Risk proportion to severity and duration of inflammation
- Cancer risk in inflammatory bowel disease (~2% risk)
- Screening recommendations:
  - First 8-10 years after diagnosis→ no increased screening
  - Years 10-20→ Every 1-3 years (shorter interval with worse disease, especially if primary sclerosing cholangitis present)
  - Years 20 onwards→1-2 years
- Treatment of dysplasia: With modern techniques, including high-definition and chromoendoscopy, most dysplasia is visible. As such, it can be completely resected endoscopically. Once a dysplastic lesion has been resected, in the absence of surrounding dysplasia, ongoing meticulous colonoscopic surveillance is appropriate. Proctocolectomy is only recommended for dysplasia if endoscopic resection is not possible, or if nonvisible high-grade dysplasia or adenocarcinoma is found

INDEFINITE FOR DYSPLASIA

- Epithelial atypia that cannot be classified as either reactive or dysplastic
- Two causes: atypia in the setting of inflammation or ulceration or surface is not present for evaluation
- Management: Treat active disease and repeat biopsy in 3-12 months

LOW-GRADE DYSPLASIA

- Enlarged, hyperchromatic, smooth, "pencillate" nuclei with nuclear stratification but maintained basal orientation (similar to sporadic adenoma), higher nuclear to cytoplasmic ratio, little to no surface maturation, abruption transition, prominent apoptoses
- Molecular: IBD-associated dysplasia shows more copy number aberrations and aneuploidy than sporadic adenomas; *TP53* mutations are frequently present early
- Management: Complete endoscopic resection if visible; otherwise proctocolectomy to exclude cancer

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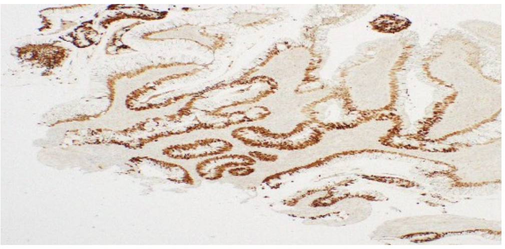
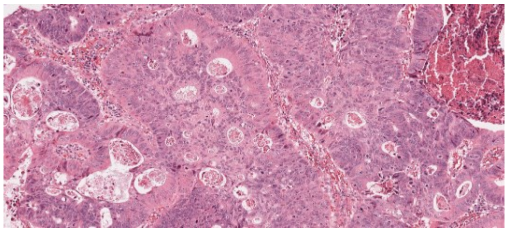
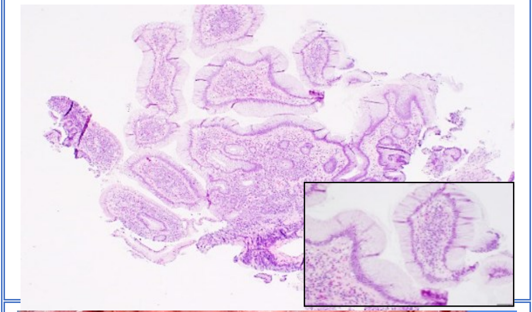
p53 IHC: overexpression in low-grade dysplasia



High-grade dysplasia with cribriform architecture



Serrated epithelial change



HIGH-GRADE DYSPLASIA

- Enlarged, hyperchromatic, pleomorphic nuclei, often plumper nuclei than low grade; irregular nuclear contours, prominent nucleoli, loss of nuclear polarity, complex architecture such as cribriforming, crypt branching/budding
- Molecular: P53 staining often highlights both grades: Dysplasia→ Strong P53 staining (or null-type) at the surface in atypical areas

NON-CONVENTIONAL LESIONS

SERRATED EPITHELIAL CHANGE

- Distorted crypt architecture with serrations at the top and bottom of crypts
- Nuclei are bland with goblet-rich epithelium
- Controversial risk of cancer; some consider it indefinite for dysplasia
- Emerging genetics, likely *TP53* mutations

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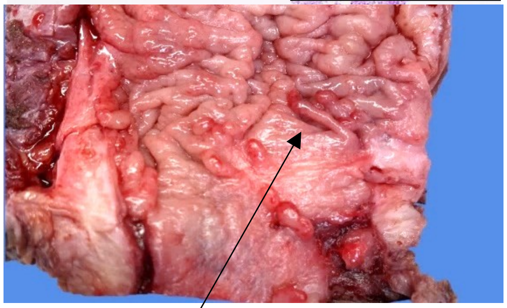
NON-CONVENTIONAL DYSPLASIA

- Hypermucinous, traditional serrated adenoma-like, sessile serrated lesion-like, Paneth cell differentiation, goblet cell-deficient, terminal epithelial differentiation

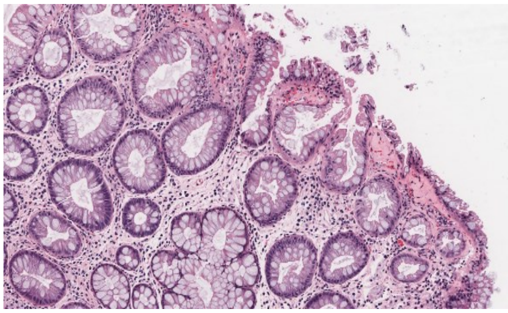


Pseudopolyps of inflammatory bowel disease

DISTINGUISHING FEATURES OF CROHN AND ULCERATIVE COLITIS

CROHN	ULCERATIVE COLITIS
Rectum spared	Rectum affected
Anal lesions in 75%	Anal lesions are rare
Deep fissures and fistulas	Horizontal fissures
Inflamed serosa	Serosa unaffected
Strictures	No strictures
Patchy transmural inflammation	Continuous, diffuse inflammation limited to mucosa/submucosa
Granulomas may be present	No granulomas

COLORECTAL EPITHELIAL POLYPS



HYPERPLASTIC POLYP

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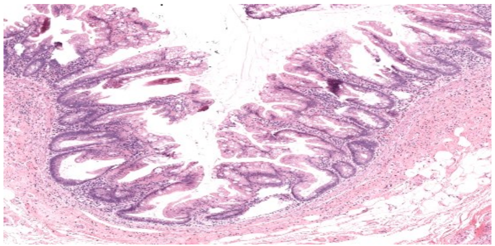
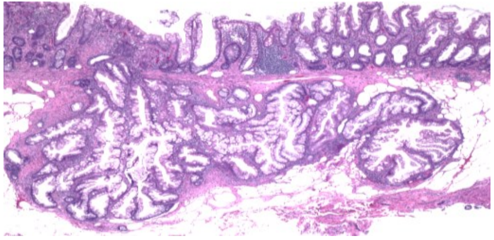
- **Serrated architecture with serrations limited to the upper half of the crypts**; mild nuclear enlargement but not as severe as conventional dysplasia; microvesicular and goblet-cell rich variants
- Soft features: Thickened subepithelial collagen, base has retained neuroendocrine cells
- Very common polyp, particularly in rectum; tend to be numerous, ≤ 5 mm
- **No significant risk of malignant transformation**
- Microvesicular variant may contain *BRAF* mutation; goblet cell rich may show *KRAS* mutation

SSL with serrations to the base





SSL with prolapse into the submucosa

SESSILE SERRATED LESION/POLYP/ADENOMA (SSL)

MORPHOLOGY

- Serrated neoplastic precursor lesion of colorectal cancer
- **Serrations extends to the base with asymmetrical growth such as boot-shaped, inverted-T;** only **one unequivocal distorted** crypt is required
- May contain fibroblastic/perineuriomatous stroma
- May develop traditional or serrated cytologic dysplasia

OTHER HIGH YIELD POINTS

- Currently referred to as sessile serrated lesion; former names sessile serrated adenoma/polyp
- Usually large (≥ 1 cm), **sessile**, **right-sided**
- Sporadic microsatellite instability pathway: Normal colon → *BRAF* V600E→ HP→ DNA methylation → SSL → MLH1 promoter methylation/deficiency → Microsatellite instability → Dysplasia → Carcinoma

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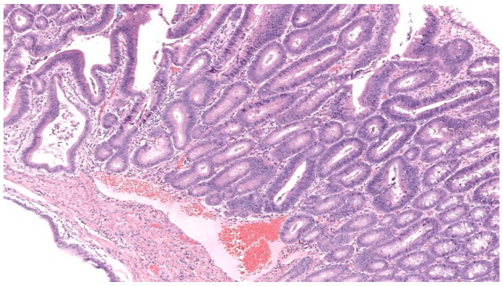
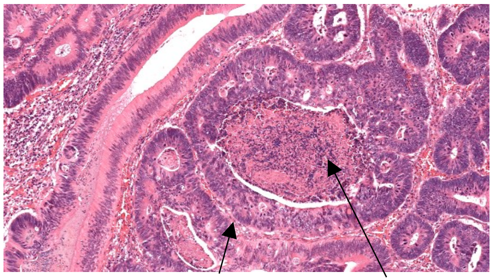
Pencillate, pseudostratified, and hyperchromatic nuclei





High-grade dysplasia: Cribriforming and necrosis

TUBULAR ADENOMA

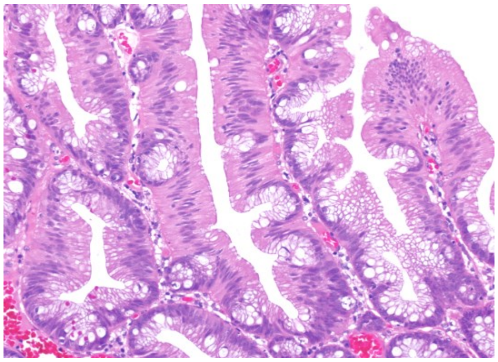
MORPHOLOGY

- Dysplasia is characterized by "picket fence" nuclei that are elongated, **pencillate, pseudostratified, hyperchromatic**
- **Low-grade dysplasia:** Nuclei remain in basal orientation (in the bottom half of the cell); changes should involve at least the upper half of the crypts and luminal surface
- **High-grade dysplasia:** Cytologic pleomorphism with rounded nuclei, increased nuclear to cytoplasmic ratio, prominent nucleoli, open chromatin **and** architectural complexity such as cribriforming, luminal necrosis
- **Intramucosal carcinoma:** Single cell infiltration into lamina propria, small irregular glands in the lamina propria (considered in-situ disease in the colorectum)

OTHER HIGH YIELD POINTS

- Variants: Tubular adenoma- greater than 75% tubules; tubulovillous adenoma- greater than 25% villi; and villous adenoma- greater than 75% villi
- **Chromosomal Instability Pathway (most common):** *APC* → *KRAS*→ *p53* (also often β-Catenin and *SMAD4*)
- **Lynch Microsatellite Instability Pathway:** Germline MMR mutation → Loss of heterozygosity → Microsatellite instability

Path Presenter



TRADITIONAL SERRATED ADENOMA

MORPHOLOGY

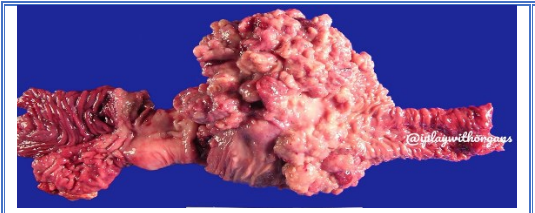
- Columnar cells with mucin depleted, **eosinophilic cytoplasm**
- Nuclei with low grade dysplasia, pencillate; **ectopic crypts** are a unique feature

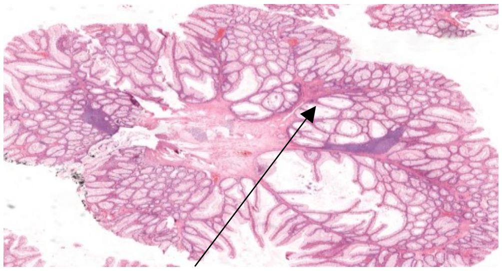
OTHER HIGH YIELD POINTS

- Uncommon
- Often pedunculated, villous, and **left-sided**
- Contain either *KRAS* or *BRAF* mutations
- Unlike hyperplastic polyps, considered cancerous

Path Presenter

5. GASTROINTESTINAL PATHOLOGY





Gross image courtesy of Cory Nash, MS, PA (ASCP)
Arborizing smooth muscle

HAMARTOMATOUS POLYPS

PEUTZ-JEGHERS POLYP

MORPHOLOGY

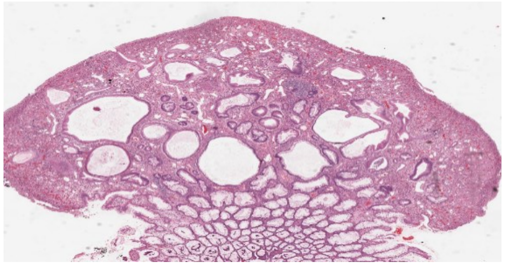
- Hamartomatous polyp (non-neoplastic) with multilobulated architecture, **arborizing smooth muscle**, and bland (non-dysplastic) epithelium

OTHER HIGH YIELD POINTS

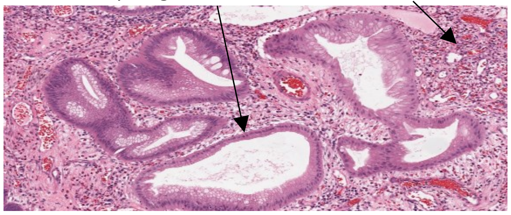
- Seen in **Peutz-Jegher's syndrome** that show germline mutation in ***STK11/LKB1*** gene (can be sporadic or inherited)
- Most frequent in the small bowel
- Additional findings of mucocutaneous **melanotic macules** (lips and oral mucosa)
- Increased risk of many cancers such as stomach, colon, pancreas, breast etc
- Additional associations- **Ovarian sex cord stromal tumor with annular tubules, sertoli cell tumors, cervical adenoma malignum**

Path Presenter

Smooth, spherical and pedunculated polyp



Cystic glands and abundant inflamed stroma



JUVENILE POLYP

MORPHOLOGY

- Hamartomatous polyp (non-neoplastic) that is smoothly spherical and pedunculated; **prominent cystic glands**, **abundant inflamed stroma without dysplasia**; surface may be eroded

OTHER HIGH YIELD POINTS

- **Most common pediatric colon polyp**
- Extremely low risk of malignant transformation unless syndromic
- Majority are solitary; multiple may indicate **Juvenile Polyposis Syndrome** (JPS)
- JPS is autosomal dominant caused by germline defect in ***SMAD4* or *BMPR1A***
- JPS is defined by ≥5 juvenile polyps or any number if positive family history
- Usually 50-200 polyps
- Can develop dysplasia and colon cancer; age at colon cancer ~35 years

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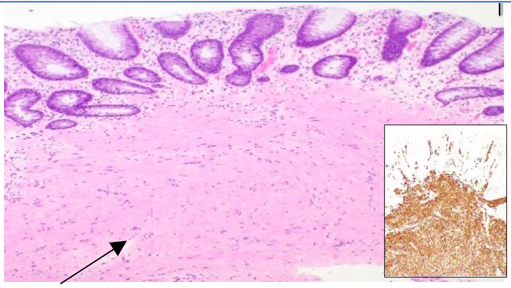
COLORECTAL MESENCHYMAL POLYPS



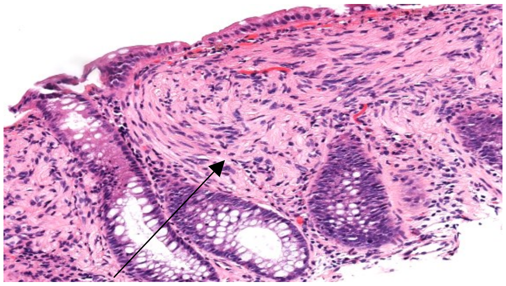
Nodular smooth muscle

Desmin +

LEIOMYOMA

- Often presents as a small submucosal polypoid mass/polyp; M>F; generally <1 cm
- In the colon, majority arise in the rectosigmoid
- Benign **smooth muscle neoplasm comprising of bland spindled cells with intersecting fascicles** and no significant mitotic activity
- IHC: **Positive for desmin** and SMA while negative for CKIT, DOG1, CD34, and S100

Path Presenter

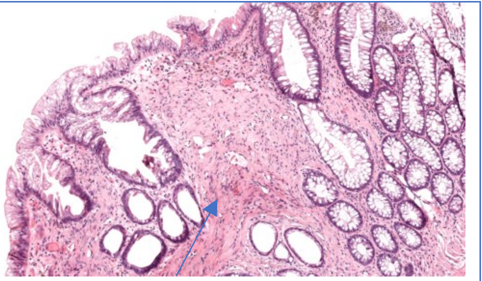


Neural cell proliferation surrounds the native crypts

SCHWANN CELL HAMARTOMA

- Benign poorly circumscribed mucosal **neural cell proliferation** that presents as a polyp; F>M; generally, < 1 cm
- No ganglion cells are present; no syndromic association
- Can arise anywhere but more common in distal colorectum
- IHC: **Positive for S100** and neurofilament while negative for EMA, SMA, CKIT, DOG1, and CD34
- Differential diagnosis: Perineurioma (EMA+) and ganglioneuroma (ganglion cells present

Path Presenter

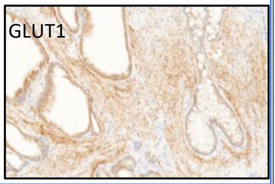


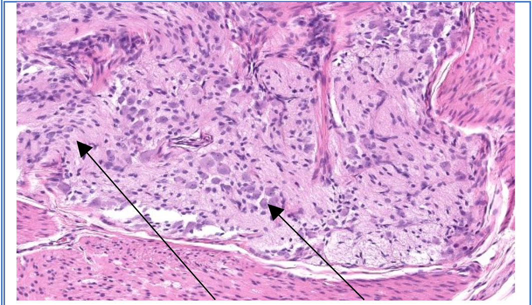
Spindle cell peirneurial proliferation, EMA+

PERINEURIOMA

- Benign polypoid **poorly circumscribed lesion** comprising of a **spindle cell perineurial proliferation,** usually confined to the mucosa
- Overlying epithelium usually shows surface hyperplastic changes or can be associated with another polyp such as a serrated polyp or tubular adenoma
- IHC: **Positive for EMA, claudin 1, CD34, and GLUT1** while negative for CKIT, desmin, and S100

Link





Neoplasm with Schwann cells and ganglion cells

GANGLIONEUROMA

- **Benign** mesenchymal polyp
- Unrelated to a similarly named lesion of the adrenal gland
- Expansion of lamina propria by bland spindled **Schwann cells** with scattered or abundant **ganglion cells**
- Multiple ganglioneuromas raise consideration for **Cowden syndrome**
- IHC: Schwann cells are positive for S100; ganglion cells are positive for S100, synaptophysin and NSE

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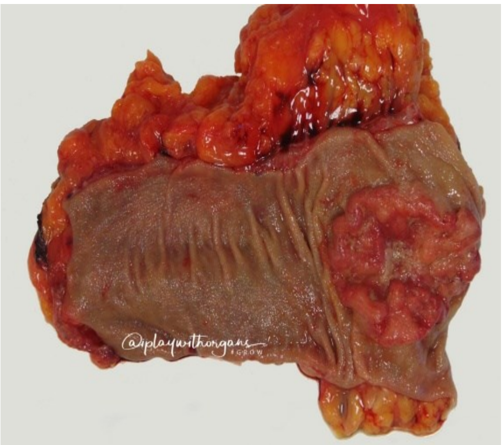
COLON/RECTUM: ADENOCARCINOMA

Adenocarcinoma, not otherwise specified



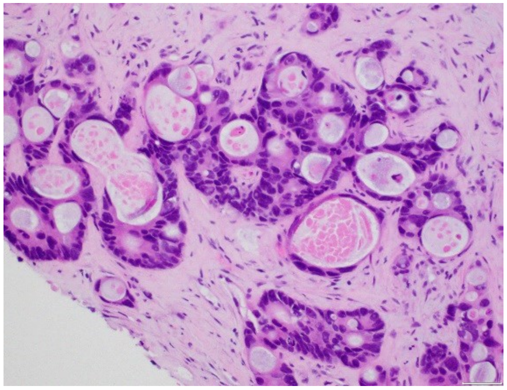
MORPHOLOGY

- Invasive adenocarcinoma is defined by the **infiltration of neoplastic glands into the submucosa**
- Single cells, desmoplastic stroma, complex architecture, and necrosis are some features that can be seen
- Grading based on gland formation: Well-differentiated (>95%), moderately differentiated (50-95% glands), poorly differentiated (<50% gland formation)
- IHC profile: Generally positive for CK20, CDX2, SATB2, and Villin while negative for CK7

OTHER HIGH YIELD POINTS

- Third most common cancer in the United States
- Associated with processed food, obesity, red meat, low fiber diet, and alcohol
- Most arise through the adenoma → carcinoma sequence

Gross image courtesy of Cory Nash, MS, PA (ASCP), Dept of Pathology, University of Chicago; used with permission



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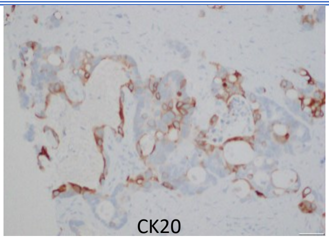
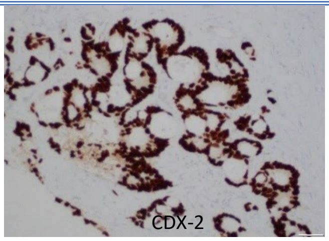
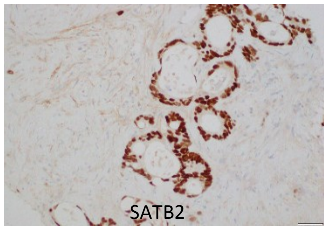
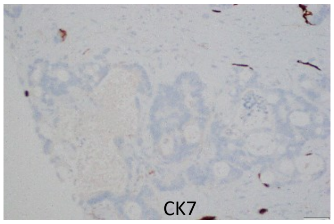
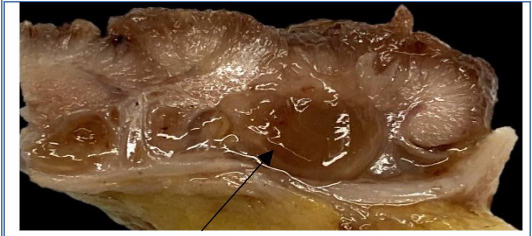


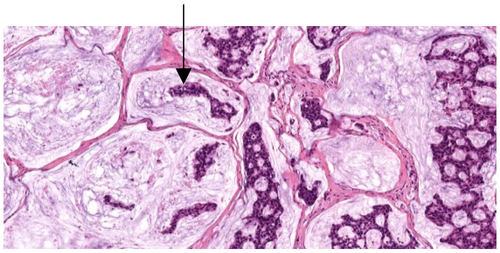




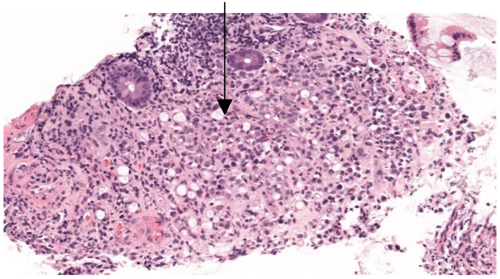




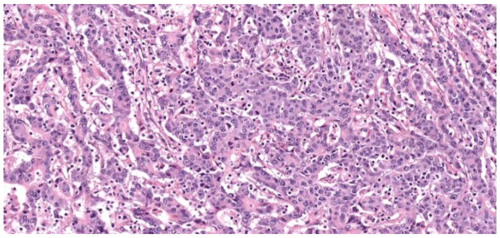
Mucinous carcinoma



Signet ring cell carcinoma



Medullary carcinoma



SUBTYPES OF CARCINOMA

- Although most colon cancers are “NOS” (Not Otherwise Specified), some subtypes exist, many of which have distinct morphology, clinical implications, and molecular alterations

MUCINOUS ADENOCARCINOMA

- >50% of tumor composed of pools of extracellular mucin (the **most common** subtype); if <50% mucin →Adenocarcinoma with mucinous features
- No prognosis implications
- Enriched for Microsatellite Instability (MSI)-high tumors

SIGNET-RING CELL ADENOCARCINOMA

- >50% of tumor is composed of signet-ring cells (prominent intracytoplasmic mucin displacing the nucleus)
- Worse outcome
- Associated with Lynch syndrome and MSI-high

MEDULLARY CARCINOMA

- Sheets of malignant cells with vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and a prominent inflammatory infiltrate
- Better prognosis
- *BRAF* mutations→ MSI-high

Path Presenter

SERRATED ADENOCARCINOMA

- Morphologically like serrated polyps

MICROPAPILLARY ADENOCARCINOMA

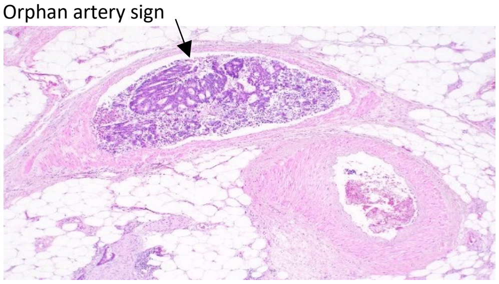
- Small clusters of tumor cells with stromal retraction
- Worse outcome (like in other organs) with early metastasis to lymph nodes

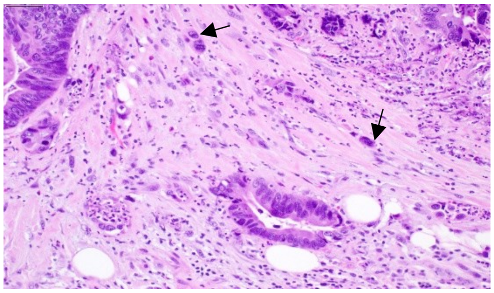
ADENOMA-LIKE ADENOCARCINOMA

- Pushing invasion with minimal desmoplasia
- Difficult to diagnose on biopsy
- Good prognosis

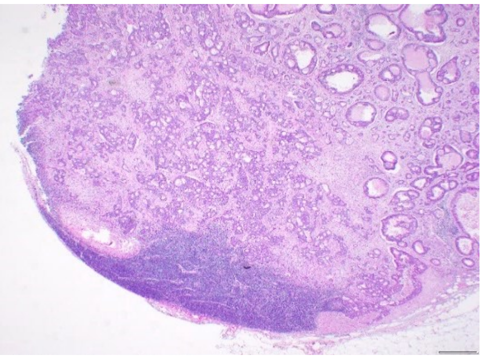
ADENOSQUAMOUS ADENOCARCINOMA

Orphan artery sign





Tumor buds (arrows)



Tumor metastasis in a lymph node

OTHER MORPHOLOGIC FEATURES

LARGE VENOUS INVASION

- Tumor involving endothelium-lined spaces with an identifiable smooth muscle layer or elastic lamina
- Difficult to diagnose on biopsy
- Extramural venous invasion (outside muscularis propria) is a risk factor for liver metastasis
- Orphan artery sign: Artery with a large, rounded tongue of tumor next to it
- EVG can highlight elastic lamina of arteries and veins

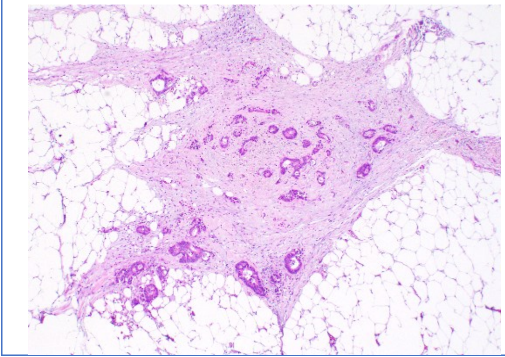
TUMOR BUDDING

- Single cells or small clusters of < 5 cells at the advancing front of the tumor
- High tumor budding is a significant risk factor for nodal involvement/poor outcome. Represents "epithelial-mesenchymal transition"

LYMPH NODE VERSUS TUMOR DEPOSITS

- Lymph node metastasis has residual lymphoid tissue surrounding it; usually rounded contour
- Tumor deposit is a focus in fat without identifiable lymph node tissue, nerve or vascular structure

Tumor deposit



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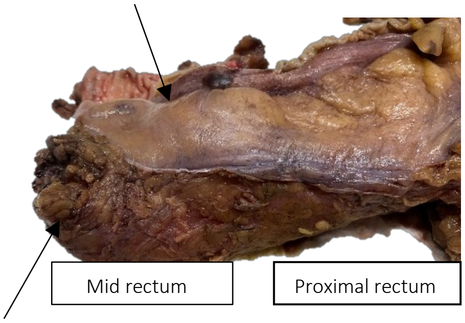
Anterior peritoneal reflection



Mesorectal fat/envelope

RECTAL CANCER: UNIQUE ANATOMIC CONSIDERATIONS

- Portion of rectum is not covered by peritoneum/serosa (anterior peritoneal reflection) but rather mesorectal fat (non-peritonealized surface)
- The quality of surgical technique/completeness of mesorectal envelope is the key determinant of local recurrence and long-term survival
- Gross assessment of mesorectal envelope: Complete (good bulk, smooth surface, no visible muscle), nearly complete (moderately bulky, minor irregularities (> 5 mm), versus incomplete (visible muscularis propria)
- Mesorectal fat radial margin/circumferential margin: Considered positive if tumor is <1 mm from inked margin

MOLECULAR PATHWAYS OF COLORECTAL CANCER

1) CHROMOSOMAL INSTABILITY PATHWAY (NON-HYPERMUTATED PATHWAY)

- ~85% of colorectal cancers
- Adenoma to carcinoma sequence; large chromosome arm gains and losses
- Common mutations: *APC* (early, starts adenoma →activates the WNT pathway), *KRAS*, and *TP53*
- *RAS* mutations (~50% of tumors)→resistant to anti-EGFR therapy (used to treat metastatic cancer)

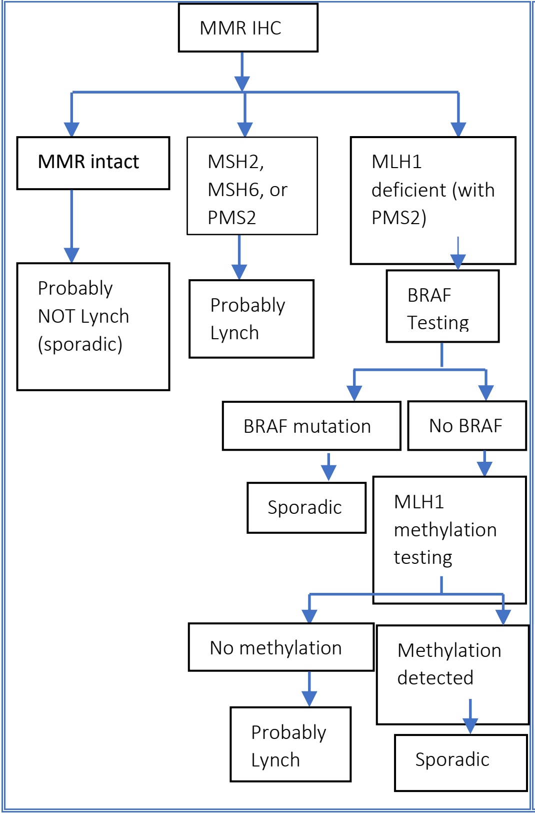
2) MICROSATELLITE INSTABILITY PATHWAY (MSI, HYPERMUTATED PATHWAY)

- ~15% of colorectal cancers
- **SPORADIC:** *BRAF* mutation → *MLH1* promoter hypermethylation → Inactivation of mismatch repair (MMR) enzymes → Serrated polyp → Carcinoma
- **LYNCH-ASSOCIATED:** Germline mutations in MMR proteins→ Loss of heterozygosity→ Adenoma → Carcinoma→ Lots of mutations → More immunogenic → More inflammatory response to tumor → Better outcome (responds to checkpoint inhibitors (e.g., anti-PD-L1 drugs))

3) ULTRAMUTATED PATHWAY

- ~3% of colorectal cancers
- *POLE* (DNA replication enzyme) mutation → Lots of mistakes with DNA replication → Ultramutated tumor

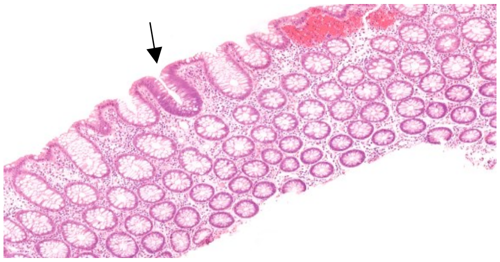
TUMOR SYNDROMES

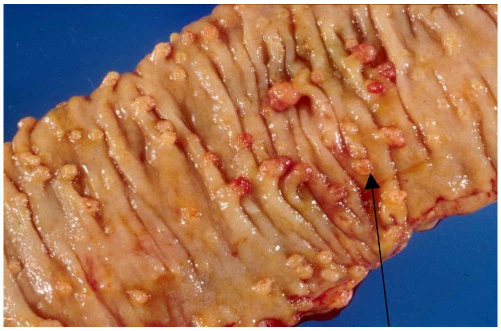


LYNCH SYNDROME (HEREDITARY NON-POLYPOSIS COLORECTAL CANCER)

- Germline mutations with mismatch repair (MMR) genes
- Autosomal Dominant → Defective DNA repair → Many mutations ("hypermutated") → Microsatellite unstable
- **Most common form of heritable colorectal cancer (CRC)**
- CRC usually develops before age 50, often with multiple primaries (~80% lifetime risk)
- Also at risk for endometrial cancer, upper urinary tract and other GI cancers, and sebaceous skin tumors
- Universal screening of all new CRC: Do IHC first (algorithm in the left tab), can also do MSI testing by PCR
- Looking for LOSS of staining. Normal is intact staining of all 4 MMR enzymes
- Lynch-related CRC is more often right-sided and arises from adenomas
- Sporadic MMR-deficient tumors, that come from sessile serrated polyps, and are associated with *BRAF V600E* mutations and then MLH-1 promoter hypermethylation and MLH1 loss of expression
- MMR-deficient CRC: Associated with **high grade, mucinous differentiation, and lymphocytic infiltrates (hypermutated state is immunogenic)**
- Better survival compared to MMR- intact CRC (probably due to host response); automatically approved for PD-L1 therapy

Unicryptal adenoma





Path Presenter Innumerable polyps in the colon

Image courtesy of: WebPathology.com, @WebPathology, used with permission

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

- Germline mutation in ***APC*** gene; Tumor suppressor → Loss leads to lots of tumors
- **Autosomal Dominant-** almost complete penetrance
- Hundreds of colorectal adenomas carpeting colon, more on left side
- Mean age of colorectal cancer diagnosis: 40 years (so often prophylactic colectomy in 20's)
- Also at risk for duodenal and gastric adenomas (less cancer risk though); need to undergo regular surveillance upper endoscopies also
- First morphologic finding: Single dysplastic crypts ("unicryptal adenoma")

VARIANTS

ATTENUATD FAP

- Less than 100 adenomas, right-sided, older age of presentation and diagnosis of cancer
- Mutation in different part of *APC* gene

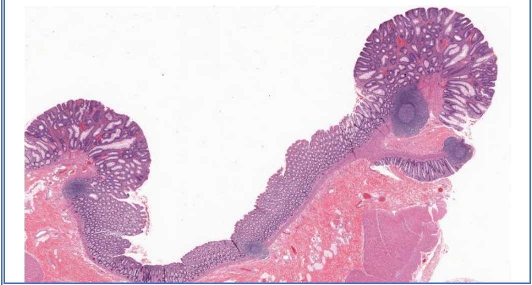
GARDNER'S SYNDROME

- **FAP with prominent extraintestinal manifestations (**including desmoid tumors, osteomas, epidermoid cysts, papillary thyroid carcinoma (classically the cribriform-morular variant), and nasopharyngeal angiofibromas)

TURCOT SYNDROME

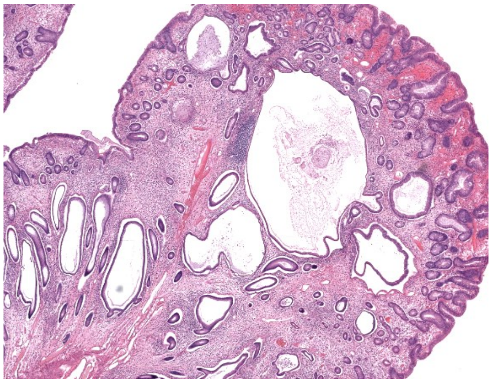
- "Glioma polyposis syndrome"- **FAP with brain tumor** (usually Medulloblastoma)

Tubular adenomas



MUTYH (or MYH) -ASSOCIATED POLYPOSIS

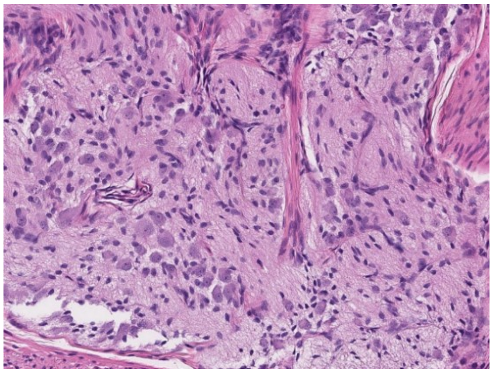
- Autosomal recessive (need biallelic germline mutations for phenotype)
- *MYH* gene is involved in base excision repair → defects result in *APC* and *RAS* mutations
- Results in multiple adenomas (usually < 100), may have extraintestinal manifestations of FAP
- Increased risk of colorectal cancer, usually right-sided, even in absence of polyps
- Differential diagnosis: HNPCC/Lynch, attenuated FAP



CRONKHITE-CANADA SYNDROME

- Uncertain etiology (NOT clearly genetic), non-familial
- Often older male (~50 years old)
- **Hamartomatous polyps** and **protein-losing enteropathy**
- Diffusely nodular mucosa throughout GI tract; broad, sessile hamartomatous polyps with edema and cystic dilations in stomach, look like hyperplastic polyps; in the colon, look like juvenile polyps
- **"Ectodermal" manifestations:** onychodystrophy, alopecia, cataracts, glossitis, vitiligo
- Increased risk of colon cancer

Path Presenter



Ganglioneuroma

COWDEN SYNDROME

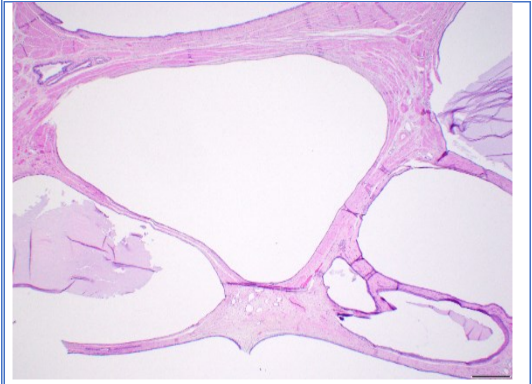
- ***PTEN* mutation;** tumor suppressor → mutation causes lots of tumors
- Autosomal dominant
- Other *PTEN* syndromes: Bannayan-Riley Ruvalcaba syndrome and Lhermitte-Duclos disease
- Associated tumors: Multiple hamartomas (mouth, GI tract), thyroid carcinoma (usually follicular), breast cancer (high risk), endometrial cancer, trichilemmomas, lipomas, glycogenic acanthosis (esophagus), hyperplastic polyps-look alikes (stomach), stroma rich polyps with cystically dilated glands mimicking juvenile polyps, mucosal lipomas (relatively unique), ganglioneuromas

ANUS

ANATOMY

- Anal canal begins where rectum enter the puborectalis sling at the apex of the anal sphincter complex (1-2 cm proximal to the dentate line)
- Anus encompasses three different mucosa types: glandular, transitional, squamous
- Dentate line is marked by transitional type mucosa and anal glands appear subjacent to the mucosa

ANUS: NON-NEOPLASTIC CONDITIONS



Tailgut cyst

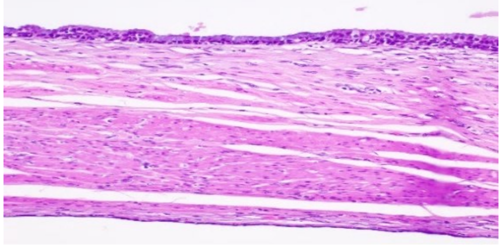
DEVELOPMENTAL AND ACQUIRED CYSTS

DUPLICATION CYST

- Lined by columnar organized gastrointestinal epithelium with a well-formed, double muscular layer and nerve plexus

TAILGUT CYST

- (Retrorectal cystic hamartoma) Cystic mass near sacrum lined by any type of gastrointestinal tract epithelium, including squamous, with disorganized smooth muscle bundles



OTHERS

- Epidermal inclusion cyst
- Median raphe cyst
- Mature cystic teratoma

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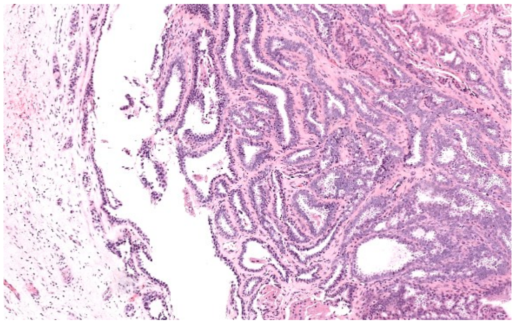


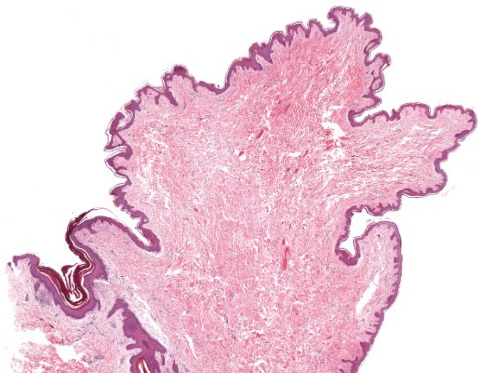
ECTOPIC BREAST TISSUE

- The "milk line" extends to the perianal area, so you can have ectopic breast tissue and even breast tumors (e.g., hidradenoma, phyllodes tumors)

HIDRADENOMA PAPILLIFERUM

- **Well-circumscribed nodule** with papillary architecture of ducts lined by a double layer of epithelial cells with decapitation secretion (**essentially the cutaneous counterpart of a breast intraductal papilloma**); apocrine features are common
- Benign neoplasm arising in the anogenital mammary-like glands, found in the vulva or perianal region
- Almost exclusively in **middle-aged women**

Path Presenter



FIBROEPITHELIAL POLYP

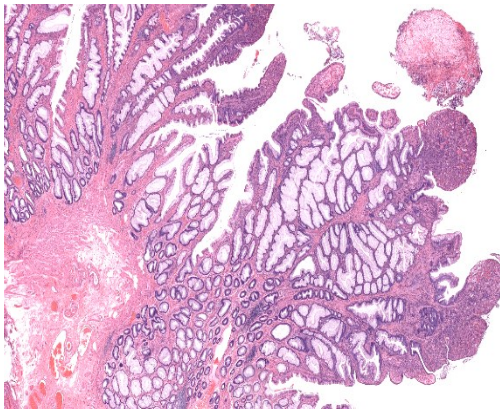
MORPHOLOGY

- Non-neoplastic polyp: Benign polypoid projections of anal squamous epithelium with underlying subepithelial hyalinized vascular stroma
- May have multinucleated giant cells or fibroblasts with bizarre nuclei (large, smudged, hyperchromatic), which are thought to be degenerative
- Often CD34+

OTHER HIGH YIELD POINTS

- Synonyms: Hypertrophic anal papillae or skin tag
- Very common; resembles hemorrhoids clinically
- Differential diagnosis: Hemorrhoids (these have large dilated vascular spaces)

Path Presenter



INFLAMMATORY CLOACOGENIC POLYP

MORPHOLOGY

- Surface may include squamous, glandular, or transition zone epithelium, which is often hyperplastic, without dysplasia
- Classic feature- fibromuscular proliferation around glands
- Stromal inflammation, surface ulceration, and granulation tissue are often present

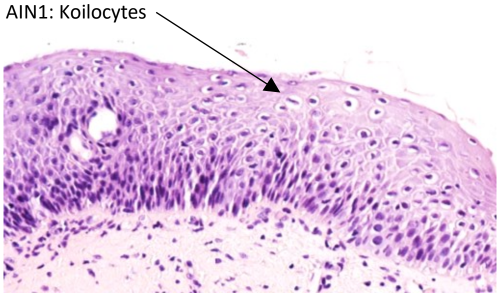
OTHER HIGH YIELD POINTS

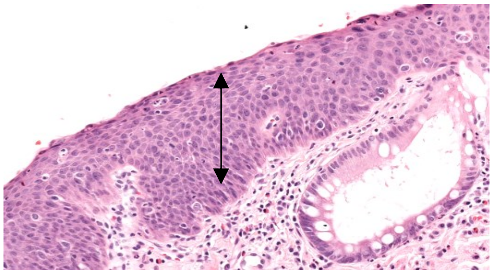
- Non-neoplastic polyp arising at the anal transition zone; may involve lower rectum, often anterior
- Thought to be due to prolapse (on a spectrum with solitary rectal ulcer syndrome and rectal prolapse)

Path Presenter

ANUS: NEOPLASTIC

AIN1: Koilocytes





AIN3: Full thickness cytologic atypia and mitoses

SQUAMOUS INTRAEPITHELIAL LESION

- Anal canal involvement: Anal Intraepithelial Neoplasia (AIN)
- Perianal skin involvement: Perianal Intraepithelial Neoplasia (PAIN)

GRADE	MORPHOLOGIC FEATURES
Low-grade, AIN1/PAIN1, Condyloma	Cytologic atypia and mitotic figures limited to the **lower 1/3rd** of epithelium with associated superficial **koilocytic atypia**; atypia meaning hyperchromatic nuclei with irregular nuclear contours Koilocytes= large superficial cells with large hyperchromatic **"raisinoid" nuclei with perinuclear halos**; cells can be multinucleated If papillomatous exophytic growth→ Condyloma; they often have epithelial thickening, parakeratosis, broad rete pegs, koilocytic atypia
High-grade, AIN 2-3/PAIN2-3	Marked cytologic atypia and superficial mitotic figures involving **full thickness (for CIS/AIN3) or up to 2/3rd thickness for AIN2**; nuclei are hyperchromatic with irregular nuclear contours; loss of architectural polarity (top looks like bottom) IHC: **Diffuse block-like p16 staining**

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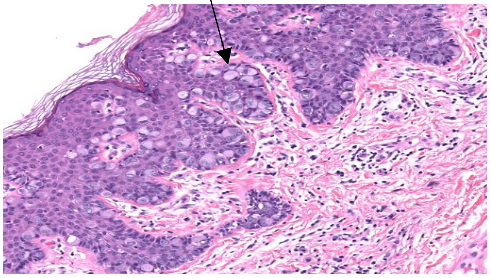
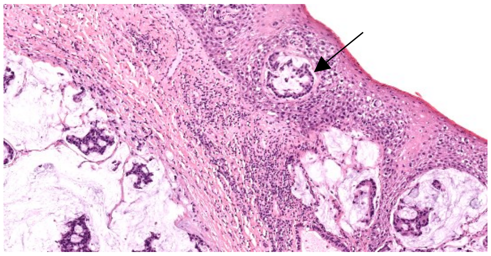
Paget's disease: Primary (no associated neoplasm)





Secondary Paget's disease with underlying anal mucinous carcinoma

PAGET'S DISEASE

MORPHOLOGY

- Pagetoid spread of malignant glandular cells within the squamous epithelium (an in-situ lesion)
- Large pleomorphic cells with abundant pale cytoplasm- may infiltrate singly or form glandular structures in the squamous epithelium
- **Primary or secondary:** Primary is not associated with an underlying neoplasm; derived from adnexal structures, has apocrine phenotype (IHC: CK7+, CK20/CDX2-, GCDFP-15/GATA-3+)
- **Secondary: Derived from an underlying rectal or anal neoplasm** (often rectal adenocarcinoma); phenotype depends on underlying malignancy (often CK20 and CDX2+)

OTHER HIGH YIELD POINTS

- Critical to differentiate primary from secondary; if primary, strong tendency to recur and can become invasive
- Differential diagnosis: Melanoma and squamous cell carcinoma in situ

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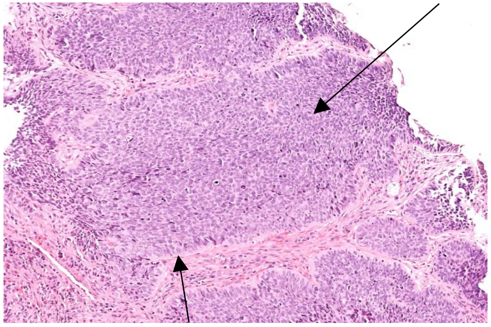
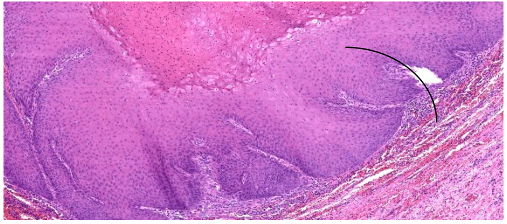
Basaloid squamous cell carcinoma: Hyperchromatic cells

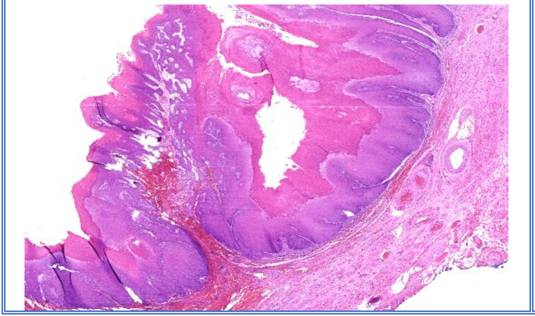


Peripheral palisading

Verrucous carcinoma: Exophytic bulbous growth



Verrucous carcinoma: pushing endophytic invasion



SQUAMOUS CELL CARCINOMA

- If a lesion can be completely visualized with gentle traction of the buttocks, it is considered a perianal lesion (not anal), which is similar to skin lesions on other parts of the body
- Carcinoma above the dentate line → metastasis to perirectal and internal iliac nodes
- Carcinoma below the dentate line → metastasis to inguinal and femoral lymph nodes

MORPHOLOGY

- Malignant epithelial tumor derived from the anal squamous mucosa with **keratin production, intercellular bridges, and frequent Human Papilloma Virus (HPV) infection**; infiltrating squamous cell clusters and strands with malignant nuclei and eosinophilic cytoplasm
- **Basaloid pattern:** Formerly called cloacogenic carcinoma; marked hyperchromasia, scant cytoplasm, and peripheral palisading (reminiscent of basal cell carcinoma)
- Admixed mucin-containing cells
- **Verrucous carcinoma:** Bland, well-differentiated thickened epithelium with bulbous exophytic fronds and endophytic "pushing" invasion; lacks HPV cytopathic effect or significant atypia; difficult to diagnose on biopsy; often associated inflammatory infiltrate; locally destructive but does not metastasize

OTHER HIGH YIELD POINTS

- Most common in older patients and women
- HPV infection in ~90% of cases (most commonly HPV type 16)
- Risk factors: Immunodeficiency (such as HIV), receptive intercourse, smoking

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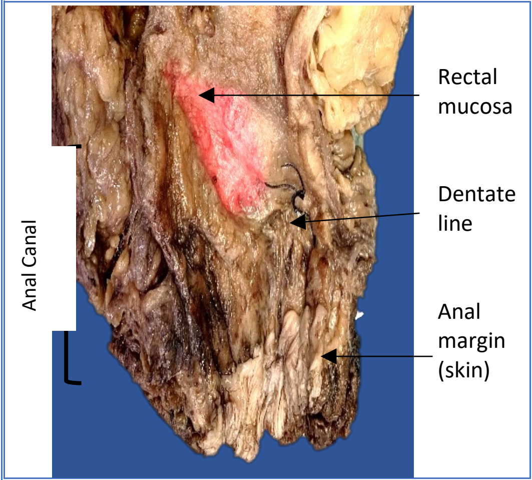
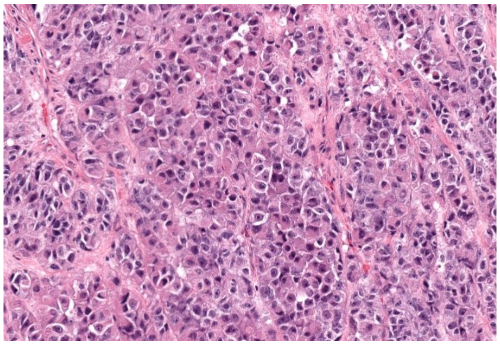


ANAL ADENOCARCINOMA

- Adenocarcinoma that arises in the anal canal; can be extramucosal or intramucosal
- **Intramucosal:** arises from luminal mucosa and is intestinal type like other colorectal cancers
- **Extramucosal** arises from anal glands, fistulas, or other structures but not overlying mucosa
- **Anal gland adenocarcinomas** arise from the anal glands/ducts; positive for **CK7 while CK20 and CDX2** negative; differential diagnosis- metastasis (such as gynecologic) and intestinal type adenocarcinoma (CK7+/-, CK20 and CDX2+)
- Most **fistula associated adenocarcinomas arise in the setting of Crohn disease and are mucinous**
- All these tumors can be associated with secondary Paget's disease


Melanoma with discohesive epithelioid tumor cells showing prominent nucleoli

MELANOMA

MORPHOLOGY

- Malignant transformation of melanocytes in the anal mucosa/ transition zone
- Polypoid mass near dentate line; typically epithelioid morphology; large, malignant cells with frequent macronucleoli, dusky greyish cytoplasm with frequent pigmentation; cells can be discohesive, plasmacytoid
- IHC: Positive for SOX10, S100, HMB45, Melan-A; Negative for cytokeratins

OTHER HIGH YIELD POINTS

- Very rare; typically affects elderly patients, more commonly women
- Molecular: *BRAF* mutations→ BRAF inhibitors (e.g., vemurafenib) and *CKIT* mutations→ tyrosine kinase inhibitors (e.g., imatinib)

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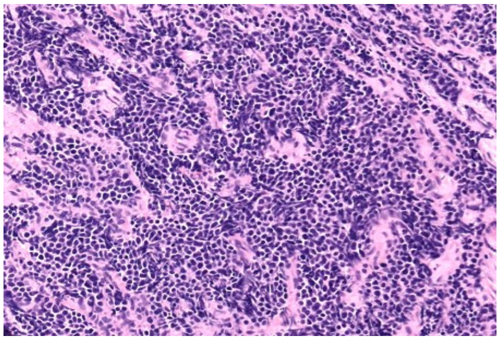
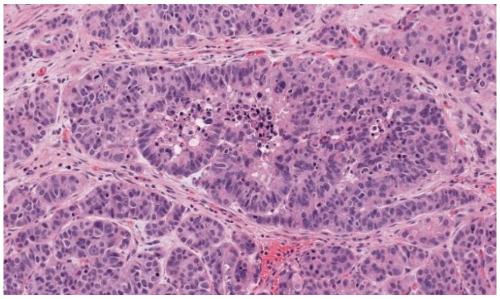
- Poor prognosis


Small cell NEC with high N:C ratio


Large cell NEC with more cytoplasm

NEUROENDOCRINE CARCINOMAS (NECs)

- **NECs are much more common in the anus than well-differentiated neuroendocrine tumors**
- NECs often arise from non-neuroendocrine tumors and subsequently develop neuroendocrine differentiation
- Two variants: Small cell type and large cell type
- Not graded as considered high-grade
- IHC: Positive for CD56, synaptophysin, chromogranin-A, INSM1; **Ki-67 tends to be >20%, often much higher**
- Molecular: Commonly ***p53* and *RB1* mutations** among others
- Treatment: Platinum based therapy

MORPHOLOGIC FEATURES

SMALL CELL NEUROENDOCRINE CARCINOMA	LARGE CELL NEUROENDOCRINE CARCINOMA
Fusiform nuclei, finely granular chromatin, scant cytoplasm, and nuclear molding, extensive necrosis, many mitoses	Large round nuclei, with prominent nucleoli, moderate amount of cytoplasm, and sheet-like or nested growth
Ki67 almost 100%	Ki67 often around 55-80%

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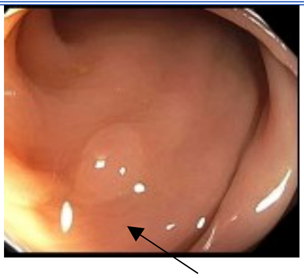
SUPPLEMENT: COLONOSCOPY SCREENING GUIDELINES

Recommended screening age for average risk individuals: 45 years

High quality colonoscopy
- Complete to the cecum
- Adequate bowel prep to detect polyps > 5 mm
- Adequate colonoscopist adenoma detection rate
- Complete polyp resection



Risk-stratified repeat colonoscopy

10 Years
- Normal colonoscopy
- ≤ 20 HPs < 10 mm

7-10 years
1-2 adenomas < 10mm

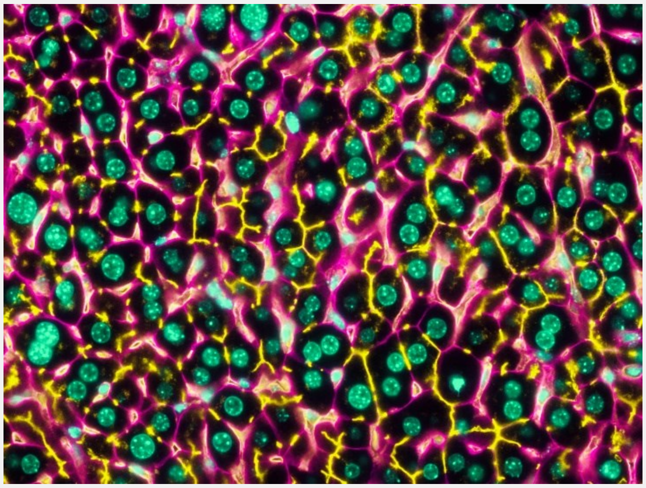
5-10 years
1-2 SSPs

3-5 years
3-4 adenomas < 10 mm
3-4 SSPs <10 mm
HP ≥ 10 mm

3 years
- 5-10 adenomas
- 5-10 SSPs
- Adenoma or SSP >10 mm
- Adenoma with villous or tubulovillous histology and/or high-grade dysplasia
- SSP with dysplasia
- Traditional serrated adenoma

1 year
> 10 adenomas

HP = Hyperplastic polyp
SSP = Sessile serrated polyp



Liver, immunofluorescence microscopy.
Image courtesy: Amy Engevik, MD

CHAPTER 6: LIVER PATHOLOGY

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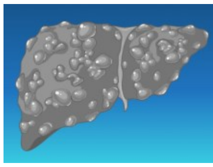
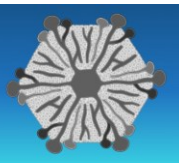
Akanksha Gupta, MD
Manju Ambelil, MD
Binny Khandakar, MD

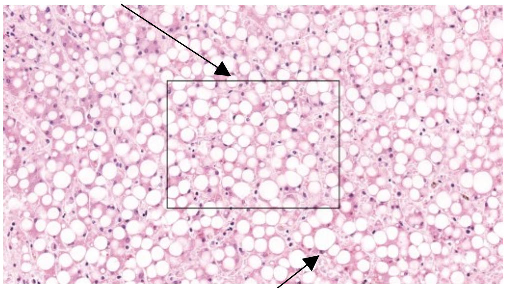


6. LIVER PATHOLOGY



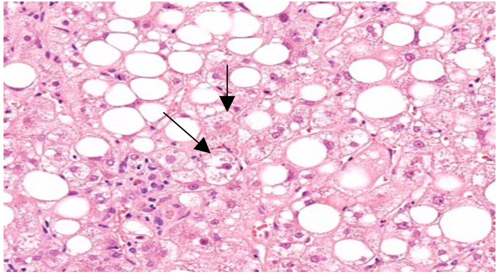
STEATOSIS/STEATOHEPATITIS

Macrovesicular steatosis

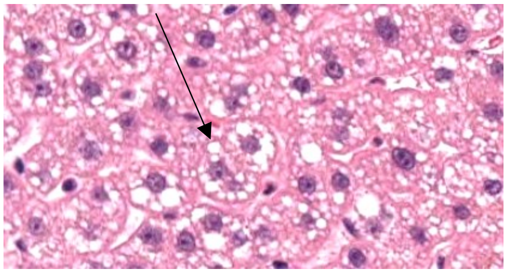


Nuclei pushed to the periphery

Ballooned hepatocytes



Microvesicular steatosis



Non-alcohol fatty liver disease (yellow gross appearance) with cirrhosis

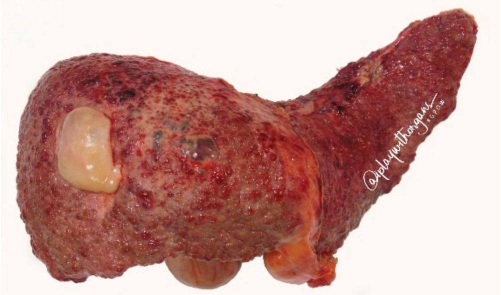
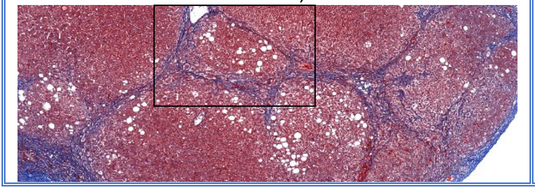


Image courtesy of: Cory Nash, MS, PA (ASCP), University of Chicago; used with permission

Cirrhosis with nodules of fibrosis, Trichrome stain



STEATOSIS/STEATOHEPATITIS

MORPHOLOGY

- **Steatosis** = Abnormal accumulation of fat within hepatocytes
- **Steatohepatitis = Fat + inflammation, acidophil bodies, and ballooning (active lobular injury)**
- These are part of the same disease process, and both lead to fibrosis, but steatohepatitis leads to fibrosis faster (essentially a difference in grading activity).
- Portal infiltrates may be present but are usually mild. If they are severe, consider additional diagnoses
- **Ballooned hepatocytes:** liver cell injury characterized by **cell swelling and enlargement** with no fat and thin, wispy cytoplasm

OTHER HIGH YIELD POINTS

MACROVESICULAR

- Represents a change in lipid metabolism
- Predominant pattern = Nucleus pushed to the side by usually a single medium to large sized droplet; smaller droplets may also be mixed in

MICROVESICULAR

- Usually represents mitochondrial injury
- Nucleus remains central with innumerable, fine fat droplets
- **Only use this term if it is a diffuse change (not focal, or in a primarily macrovesicular case)**

QUANTIFYING FAT

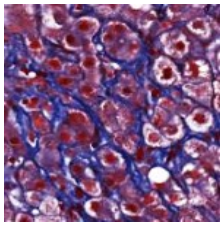
- Estimate the % of cells with macrovesicular steatosis in the entire specimen
- Often starts in zone 3

Amount of Fat	Grade
• <5%	• Normal
• 5-33%	• Mild
• 34-66%	• Moderate
• >67%	• Severe

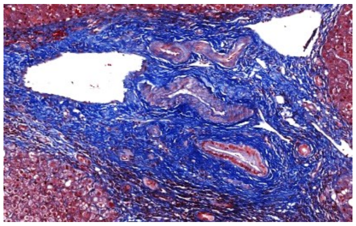
FIBROSIS

- Fatty liver disease causes **pericellular, pericentral fibrosis first** (where the most fat is)
- Progresses to portal and pericentral fibrosis
- Bridging fibrosis
- Cirrhosis, once cirrhotic, there may be relatively little fat

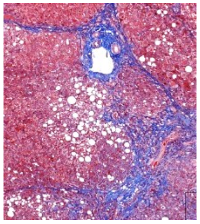
Pericellular fibrosis



Portal Fibrosis



Bridging fibrosis



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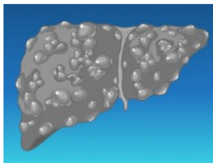
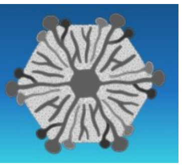
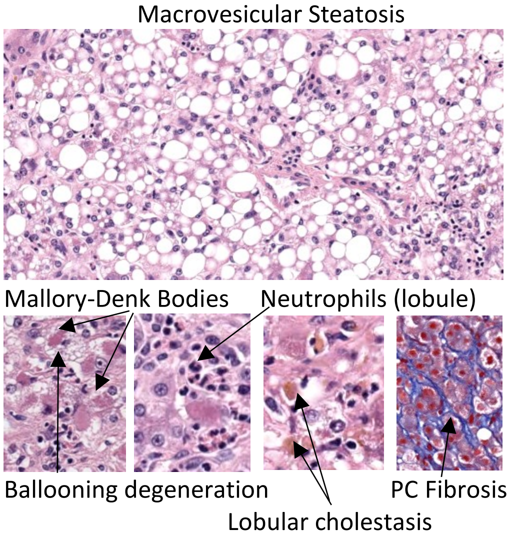


6. LIVER PATHOLOGY





ALCOHOLIC HEPATITIS

MORPHOLOGY

- Hepatocyte injury and inflammation resulting from chronic alcohol consumption
- H&E: Macrovesicular steatosis. **Findings that Favor EtOH**: More hepatocyte ballooning, more neutrophilic lobular inflammation, more Mallory-Denk bodies, lobular cholestasis, and more diffuse pericellular (PC) fibrosis
- **Mallory-Denk Bodies** = pink, ropey cytoplasmic inclusions = ubiquitinated cytokeratins (positive for p62, ubiquitin, CK18); Ballooned hepatocytes are negative for CK18.
- **But Histology can be identical to NASH!**

OTHER HIGH YIELD POINTS

- AST/ALT ratio typically >2

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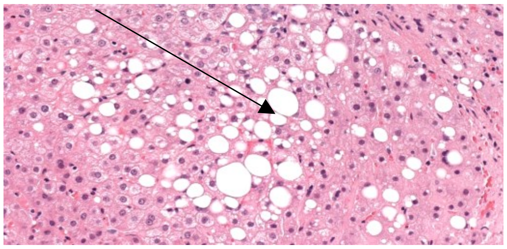
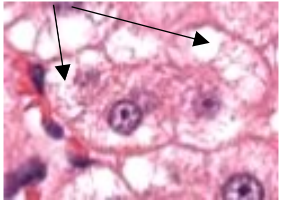
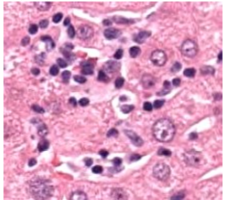
Macrovesicular Steatosis



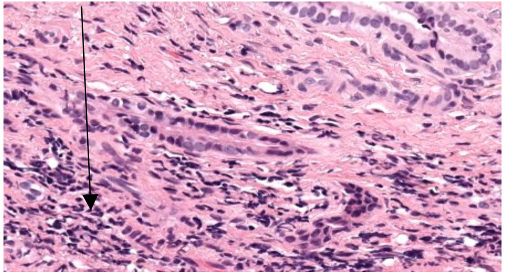
Ballooning



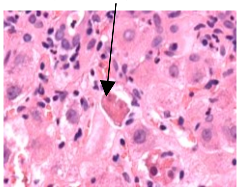
Lobular lymphocytes



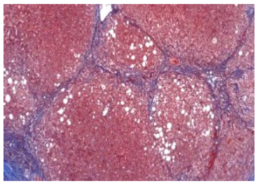
Portal inflammation (sometimes, usually mild)



Acidophil body



Cirrhosis



NON-ALCOHOLIC STEATOHEPATITIS (NASH)

MORPHOLOGY

- H&E: **Steatosis, ballooning,** lobular lymphocytes and neutrophils (exception in pediatric patients, where the inflammation is more portal), acidophil bodies, **pericellular fibrosis**
- Sometimes adults have mild portal inflammation, mainly lymphocytes

OTHER HIGH YIELD POINTS

Staging of fibrosis using NASH-CRN system

FIBROSIS	
0	None
1a	Mild zone 3 sinusoidal fibrosis
1b	Moderate zone 3 sinusoidal fibrosis
1c	Portal fibrosis only
2	Zone 3 sinusoidal fibrosis and portal fibrosis
3	Bridging fibrosis
4	Cirrhosis

Grading using the NASH-CRN system

Steatosis	Lobular Inflammation	Hepatocellular Ballooning
0: <5%	0: None	0: None
1: 5-33%	1: <2 foci/20x field	1: Mild, few
2: 34-66%	2: 2-4 foci/20x field	2: Moderate-marked, many
3: >66%	3: >4 foci/20x field	

- Sum the individual components for a total grade (maximum of 8)

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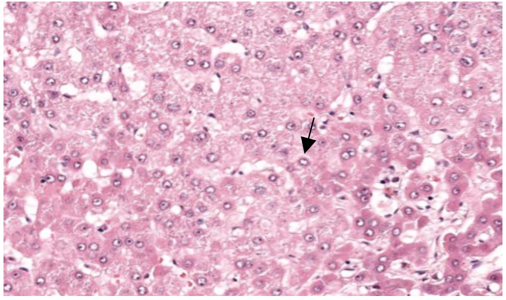
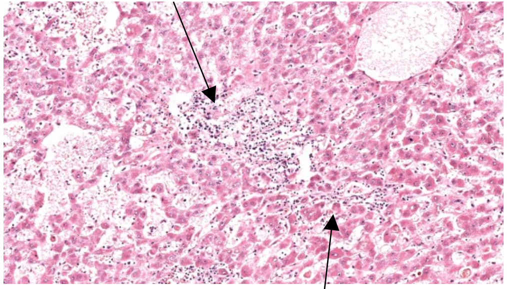




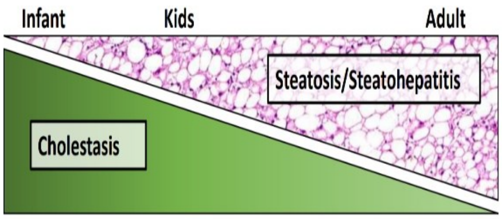
WILSON'S DISEASE

MORPHOLOGY

- Variable.
- Can present as acute hepatitis, fulminant hepatitis, chronic hepatitis, or cirrhosis
- **Steatohepatitis, possible Mallory-Denk bodies, and glycogenated nuclei**
- Later chronic hepatitis with mild chronic portal inflammation (predominantly lymphocytic with some plasma cells) with interface activity and cirrhosis

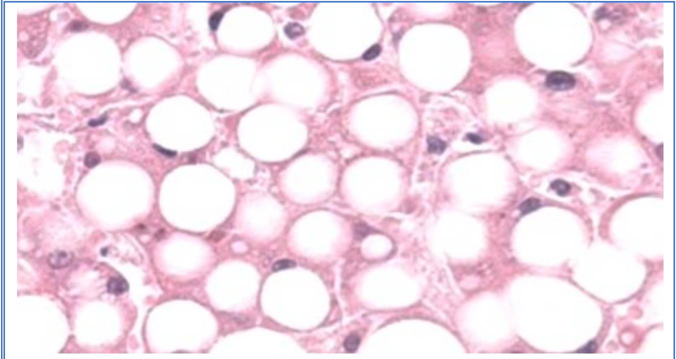
OTHER HIGH YIELD POINTS

- Mutations of **copper transport protein (*ATP7B* gene)** results in the inability to excrete copper in bile → accumulate copper in the liver and other tissues
- Variable presentation: **Acute or chronic liver disease, neurologic/ psychiatric findings, hemolytic anemia, ± Kayser-Fleischer rings**
- Labs: **Low ceruloplasmin**, Increased urine copper, AST/ALT ratio >2.2, Alk Phos/T. Bili <4
- When considering diagnosis, send tissue block for copper quantification



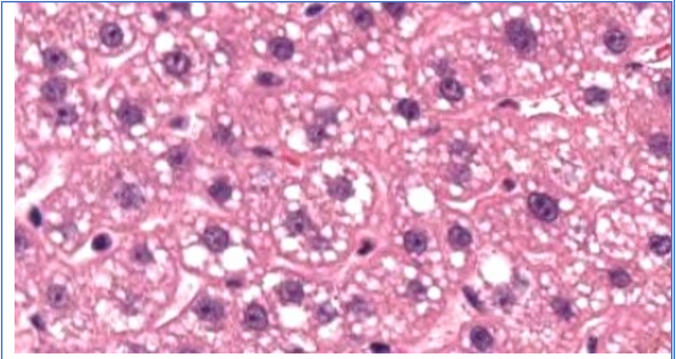
TOTAL PARENTAL NUTRITION (TPN)

- Long-term TPN can lead to liver injury
- Etiology: Unclear, multifactorial
- Histology is variable: Steatosis/steatohepatitis or cholestasis depending on age; cholestasis is more common in neonates than adults; steatosis/steatohepatitis more common in adults
- Can lead to significant fibrosis if TPN is continued
- Severe cases may require liver/small bowel transplant



OTHER CAUSES OF MACROVESICULAR STEATOSIS

- Drugs including **Amiodarone**, Glucocorticoids, **methotrexate**, tamoxifen, and certain chemotherapeutic agents
- Other conditions, including malnutrition (marasmus or kwashiorkor) (e.g., hypothyroidism, elevated cortisol, growth hormone deficiency), cystic fibrosis



OTHER CAUSES OF MICROVESICULAR STEATOSIS

- **Reye's syndrome**, inborn errors of metabolism, Drugs, Toxins, **Acute fatty liver of pregnancy**

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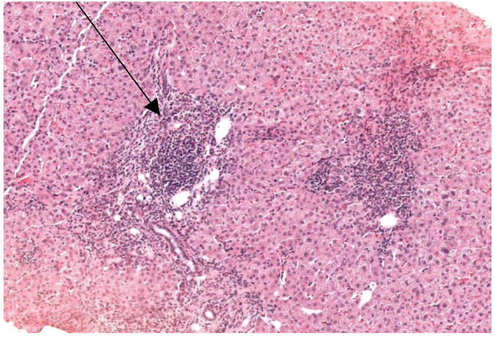
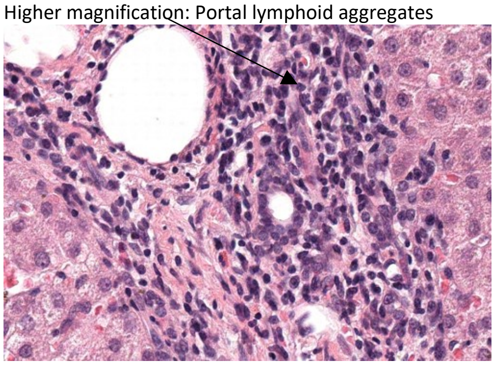
6. LIVER PATHOLOGY

PORTAL TRACT CHRONIC INFLAMMATION

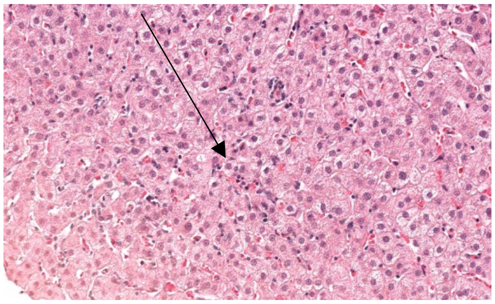
Portal infiltrates and interface activity



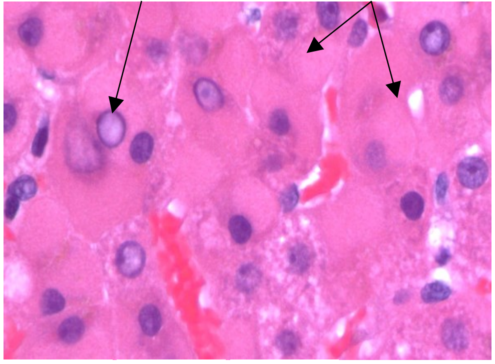
Higher magnification: Portal lymphoid aggregates



Scattered lobular inflammation



Hepatitis B: Sanded nuclei Ground glass hepatocytes



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CHRONIC HEPATITIS C

MORPHOLOGY

- Variably **dense portal lymphocytic infiltrates**; few plasma cells can be seen
- **Periportal interface activity**
- Scattered lobular collections of inflammatory cells ± acidophil bodies

OTHER HIGH YIELD POINTS

- **~90% develop chronic infection; blood borne**
- Antibodies (anti-HCV) indicate exposure
- Detection of HCV RNA indicates virus persistence
- Slow, silent, progressive disease (over decades) → cirrhosis (risk of HCC)
- Newer medications: Ledipasvir/sofosbuvir(Harvoni) →highly effective

VIRAL HEPATITIS: DISTINGUISHING ACUTE VS CHRONIC

- Often use clinical definition = elevated liver enzymes for ≥6 months
- Fibrosis also indicates chronic damage
- Diffuse moderate lobulitis means acute or acute-on-chronic
- Stage viral hepatitis using Batts-Ludwig, Ishak, Scheuer, or METAVR systems (reasonably similar)

CHRONIC HEPATITIS B

MORPHOLOGY

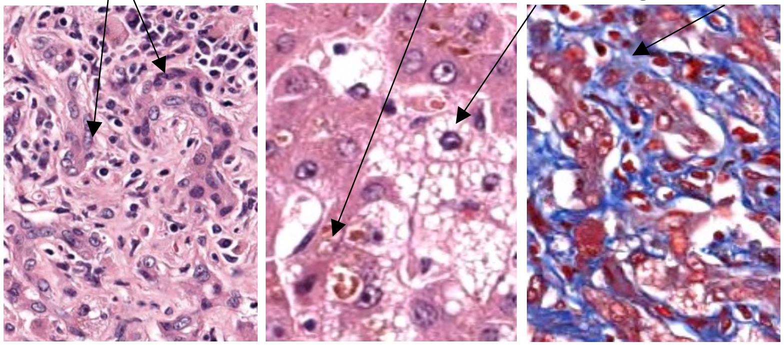
- Portal chronic inflammatory infiltrates with interface activity and lobular inflammation
- **Ground glass hepatocytes** (eosinophilic cytoplasm due to HBsAg) (cytoplasmic) and **sanded nuclei** (HBcAg excess in nuclei)
- HBsAg= infected, HBcAg= actively replicating

OTHER HIGH YIELD POINTS

- **~10% develop chronic** disease; **blood borne**

FIBROSING CHOLESTATIC HEPATITIS B

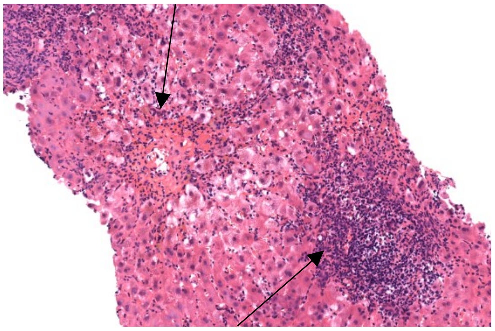
- Variant with more progressive/worse disease
- **Usually immunosuppressed state** (e.g., post-transplant)
- Bile ductular reaction, extensive cholestasis, cell swelling, and fibrosis



HEPATITIS D

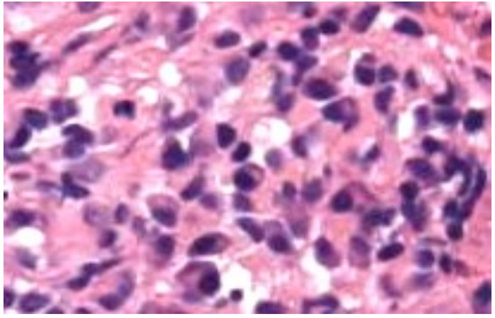
Requires Hep B infection →acute-on-chronic hepatitis

Centrivenular chronic inflammation

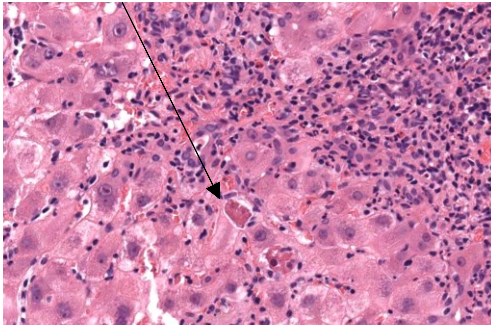


Dense portal infiltrates

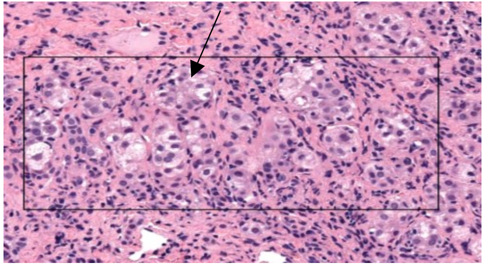
Plasma cells are conspicuous

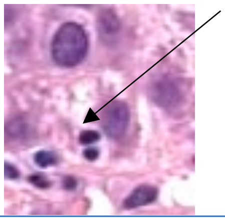


Hepatocyte apoptosis



Regenerative rosette





Emperipolesis

Path Presenter

AUTOIMMUNE HEPATITIS

MORPHOLOGY

- **Dense portal infiltrates** with marked interface activity → **lymphocytes and plasma cells**
- Lobular injury including **centrivenular inflammation** and apoptotic hepatocytes
- Regenerative rosette formation
- Can have "Overlap" with primary biliary cholangitis

OTHER HIGH YIELD POINTS

- Strong **female** predominance
- Elevated AST/ALT (often marked)
- Serology: Positive **Anti-Smooth Muscle Antibody, ANA,** LKM-1, Elevated IgG

Finding	Cutoff	Points
Autoantibodies (maximum 2 points!)		
ANA or SMA	≥ 1:40	1
ANA or SMA	≥ 1:80	2
LKM-1	≥ 1:40	2
SLA	Positive	2
Serum IgG		
	> Upper limit of normal	1
	> 1.10 times the upper limit of normal	2
Histology		
	No evidence of hepatitis	Disqualifying (Not AIH!)
	Atypical for AIH	0
	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis		
Viral serology all negative		2

Histology:

Typical:

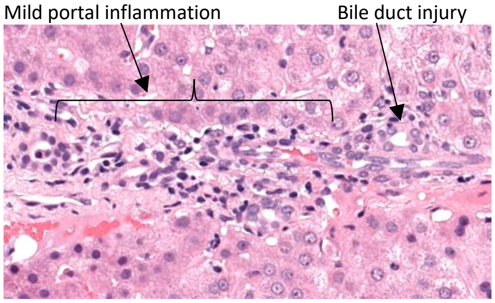
1) Lymphoplasmacytic interface hepatitis extending into the lobule
2) Regenerative rosette formation
3) Emperipolesis

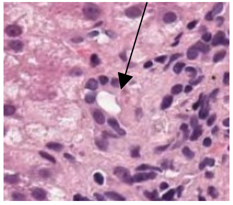
Compatible: Chronic hepatitis with lymphocytic infiltration without all the features considered typical

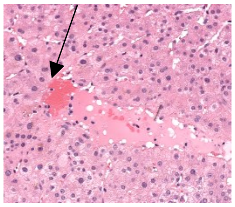
Atypical: Signs of another diagnosis, such as steatohepatitis

Scoring: ≥6: Probable AIH ≥7: Definite

Modified from Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169-76.







GRAFT-VS-HOST DISEASE (GVHD)

MORPHOLOGY

Early phase

- **Damage to bile duct epithelium:** cytoplasmic swelling and vacuolation, withering, drop out; enlarged, overlapping nuclei, and apoptosis
- Mild portal chronic inflammation
- **Possible endothelitis**

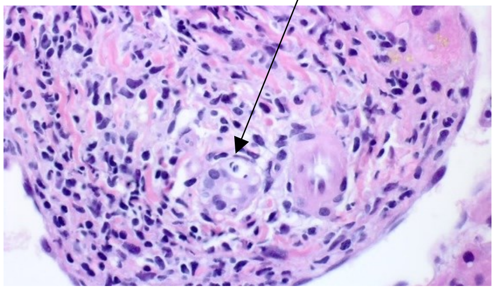
Late phase

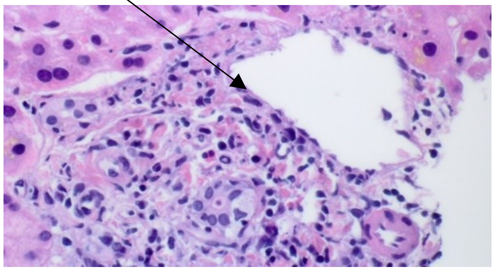
- **Loss of bile ducts**, increased fibrosis

OTHER HIGH YIELD POINTS

- Usually post-stem cell transplant (transplanted immunocompetent T-cells attack new host)
- Involves skin, liver, GI tract → rash, ↑liver function enzymes, diarrhea, and vomiting

Path Presenter





Images courtesy of Dr. Ronald Miick, Cooper University Hospital, NJ

Chronic rejection: Foam cell arteriopathy

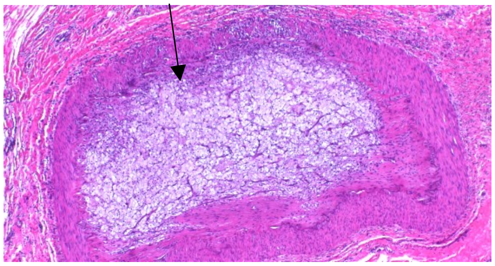


Image courtesy of Dr. Moghimi Ali, New South Wales

REJECTION

- Immune-mediated inflammation/damage in transplanted liver; usually targets bile ducts and vessels

T cell-mediated rejection

- Formerly called acute cellular rejection
- Mixed portal inflammation (lymphocytes, eosinophils), **bile duct injury**, and **endotheliitis**

Plasma cell-rich rejection

- Formerly called de novo autoimmune hepatitis
- **Portal and/or central plasma rich (>30%) infiltrates and lymphocytic cholangitis**
- Difficult to diagnose if patient carries a diagnosis of autoimmune hepatitis previously

Chronic rejection

- Bile duct injury →**eventual loss/paucity**; also lose hepatic arterioles
- Chronic vascular damage **with foam cell arteriopathy and luminal narrowing**

Antibody-mediated rejection

- **Positive serum Donor Specific Antibody (DSA)**
- Portal vascular dilatation, endothelial hypertrophy, **arteritis,** edematous portal tract, and cholestasis
- Positive **C4d IHC** showing staining in >50% veins and capillaries

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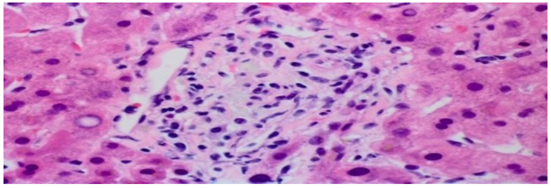
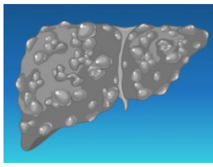
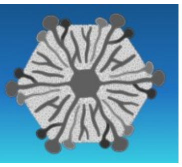
Chronic rejection: Portal tract with absent bile duct





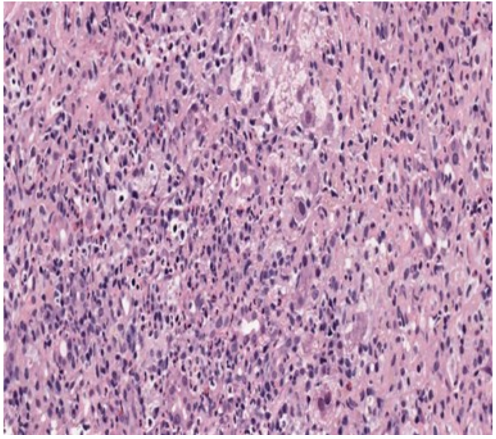
6. LIVER PATHOLOGY



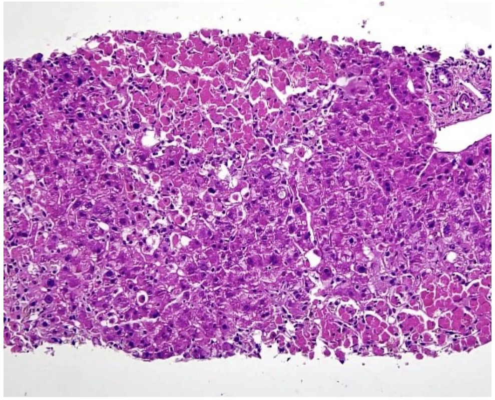
LOBULAR INJURY

- Indicates an **acute process** (too injurious to be chronic!) and often patient has very high transaminases
- Features: Lobular disarray (normal plate structure disrupted), **lobulitis** (lymphocytes attacking hepatocytes in lobule), conspicuous **acidophil bodies** (apoptotic hepatocytes)

Acute viral hepatitis



Acetaminophen toxicity



ACUTE VIRAL HEPATITIS

MORPHOLOGY

- Lobular damage and disarray, **diffuse lobular inflammation** rich in lymphocytes, plasma cells, histiocytes, hepatocyte swelling and necrosis
- May see **mild** portal and periportal inflammation
- **No fibrosis**

OTHER HIGH YIELD POINTS

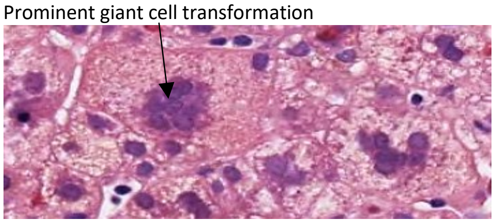
- Largely a clinical term used with elevation in liver associated enzymes of <6 months duration
- **Most common cause is hepatotropic viruses** such as hepatitis A, B, E (acute infections are subclinical in hepatitis C); hepatitis A and E are spread by fecal-oral ("the vowels hit the bowels")
- **Drugs/toxins, Wilson disease, and early autoimmune hepatitis** can present with this pattern
- Diagnosis for viruses confirmed by serology or serum PCR

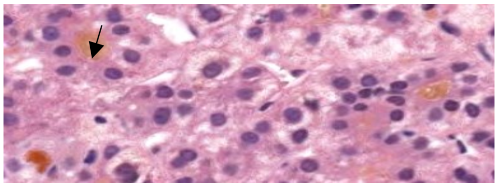
DRUG REACTION

- Two chief mechanisms: **Intrinsic** (predictable, dose-dependent, less inflammation, more necrosis) vs. **idiosyncratic** (majority of cases, not dose-dependent, more inflammation)
- **Tylenol causes intrinsic injury with extensive zone 3 necrosis and minimal inflammation due to N-acetyl=p-benzoquinone imine (NAPQI) accumulation**; treatment: **N-acetylcysteine**
- Very diverse findings that can **mimic** other disorders such as **autoimmune hepatitis**; clinical context is key
- Herbal and botanical drugs are important but often overlooked cause of hepatotoxicity

Link Link

Prominent giant cell transformation





Canalicular cholestasis

IDIOPATHIC NEONATAL HEPATITIS (AKA NEONATAL GIANT CELL HEPATITIS)

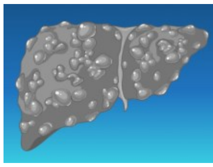
MORPHOLOGY

- Lobular disarray with prominent giant cell transformation
- Absent to mild lobular inflammation (despite name); canalicular and hepatocellular cholestasis; minimal portal tract changes and preserved bile ducts

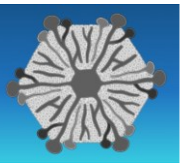
OTHER HIGH YIELD POINTS

Path Presenter

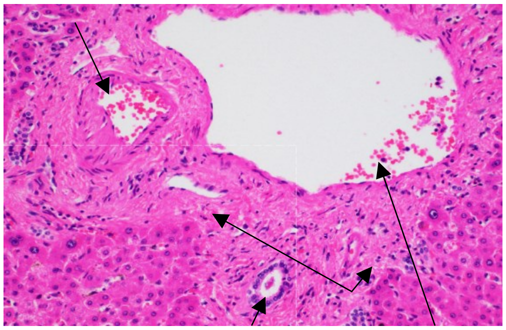
- Neonatal jaundice with hepatomegaly
- Elevated total bilirubin and conjugated bilirubin
- Variable AST/ALT
- Diagnosis of exclusion (must exclude biliary atresia)
- Loose association with hypopituitarism

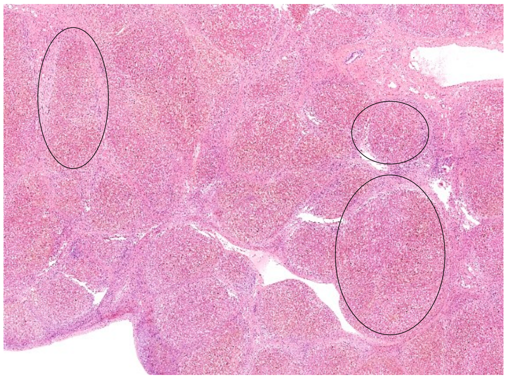


6. LIVER PATHOLOGY



BILIARY DISEASES





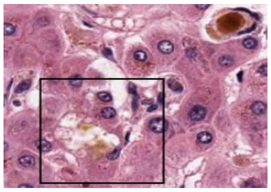
Regenerative nodules with jig-saw fibrosis of variable size (irregular)

BILIARY/CHOLESTATIC PROCESSES

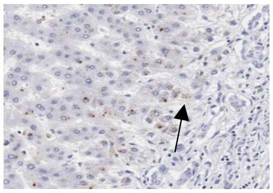
- Laboratory findings: Elevated Alkaline Phosphatase (ALP), Gamma-glutamyl Transferase (GGT), and Bilirubin
- Bile ducts highlighted with CK7 and CK19
- Increased copper deposition in periportal hepatocytes
- Chronic biliary injury leads to CK7-positive staining in periportal hepatocytes that are usually negative
- Chronic biliary injury can lead to biliary-type cirrhosis
- Biliary-type cirrhosis: Jig-saw pattern of fibrosis with irregularly sized regenerative nodules
- Additional clues to biliary type cirrhosis: Cholate stasis, ductopenia, periductal fibrosis, bile infarcts

BILIARY FIBROSIS STAGING (LUDWIG'S)	
I	Inflammation restricted to portal areas and non-suppurative destruction of bile ducts
II	Ductular proliferation, an inflammatory process extending to the interface with hepatic parenchyma
III	Septal and bridging fibrosis
IV	Cirrhosis

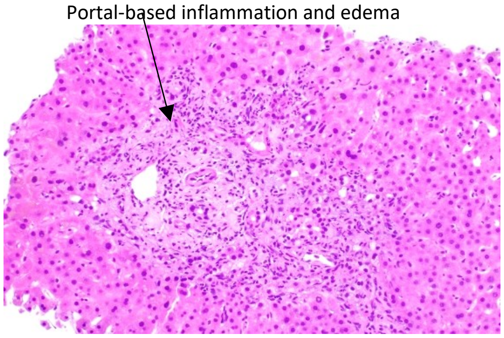
Path Presenter

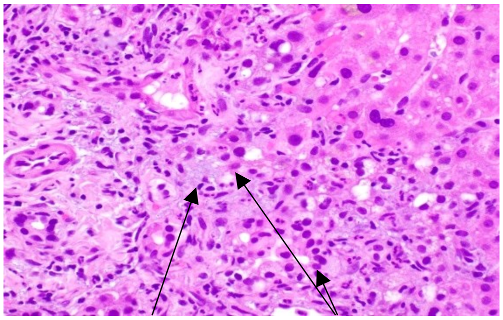


Cholate stasis



Cooper staining in periportal hepatocytes





LARGE DUCT OBSTRUCTION

MORPHOLOGY

- H&E: **Portal tract edema, portal-based mixed inflammation with prominent neutrophils, bile ductular reaction**
- Canalicular and /or ductular cholestasis
- No lobular injury/ hepatocyte apoptosis
- No fibrosis in acute biliary flow obstruction; chronic obstruction can lead to fibrosis (more fibrotic portal tract and less edema in chronic cases)

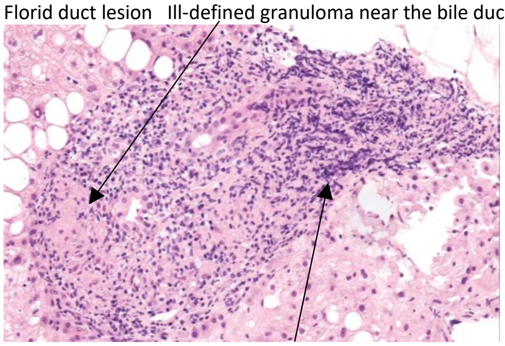
OTHER HIGH YIELD POINTS

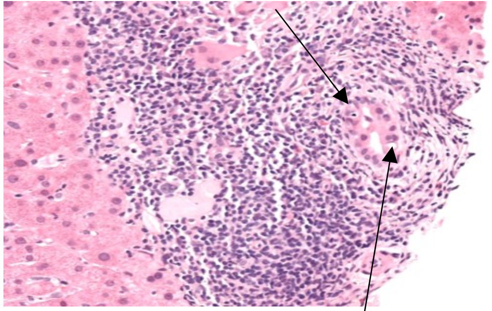
- Etiology: **Mechanical blockage of bile ducts** due to gallstones, strictures, tumors
- Usually diagnosed using imaging

Differential diagnosis:

- Ascending cholangitis (requires prominent neutrophils in the bile duct epithelium and/or lumen)
- Marked hepatitis/extensive necrosis can be associated with bile ductular reaction as part of lobular regeneration

6. LIVER PATHOLOGY


Florid duct lesion
Ill-defined granuloma near the bile duct
Moderate portal-based chronic inflammation


Bile duct injury with intraepithelial lymphocytes
Epithelial injury with vacuolization (space in the cytoplasm)

PRIMARY BILIARY CHOLANGITIS/PRIMARY BILIARY CIRRHOSIS (PBC)

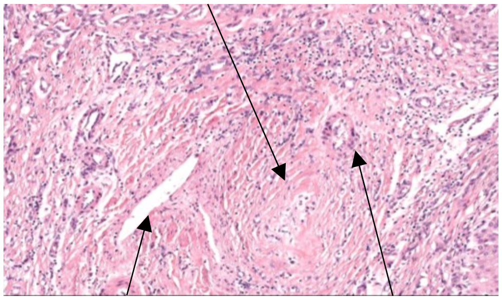
MORPHOLOGY

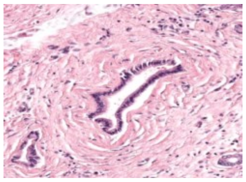
- H&E: Moderate portal-based chronic inflammation with **lymphocytes injuring the bile duct epithelium (lymphocytic cholangitis), vague non-necrotizing granulomas near the bile duct**
- May be associated with bile ductular reaction, scattered portal eosinophils; **late-stage disease has bile duct loss**
- **Florid duct lesion:** Lymphocytic cholangitis, bile duct injury ± granulomas
- Can develop cirrhosis with increased risk of hepatocellular carcinoma

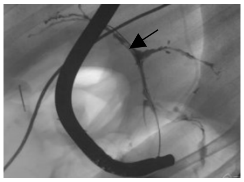
OTHER HIGH YIELD POINTS

- Autoimmune disease with inflammatory destruction of intrahepatic bile ducts
- **Associated with other autoimmune conditions**: Sjögren, thyroiditis, scleroderma, rheumatoid arthritis, lupus, celiac disease
- Symptoms can be insidious: **pruritis**, malaise, **dark urine, light stools**
- Demographic: **Middle-aged females** of Northern European ancestry
- Laboratory abnormalities: Elevated Anti-Mitochondrial Antibody **(AMA)-M2 fraction (in 95% of patients)** and elevated IgM

Path Presenter


Fibrous obliteration of the bile duct
Native portal vein
Native hepatic artery


Periductal fibrosis


ERCP shows strictures

PRIMARY SCLEROSING CHOLANGITIS (PSC)

MORPHOLOGY

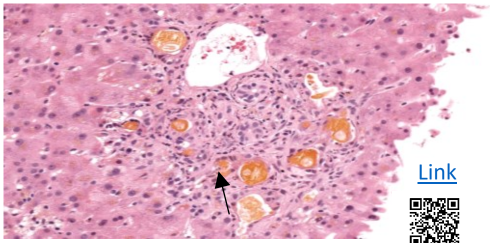
- Characteristic feature- **Stricturing of bile ducts (concentric periductal fibrosis aka "onion skin fibrosis")**
- Disease commonly affects **large extrahepatic bile ducts**; therefore, on biopsy, changes are similar to large bile duct obstruction, such as portal edema, mixed inflammation, and bile ductular proliferation
- End stage: **Fibrous obliteration of the duct lumen and ductopenia**

OTHER HIGH YIELD POINTS

- Usually diagnosed using imaging: **Cholangiography shows multiple biliary strictures (extrahepatic)**
- Associated with **increased risk of cholangiocarcinoma**
- **Strong association with ulcerative colitis**; frequently in young to middle-aged men

Path Presenter

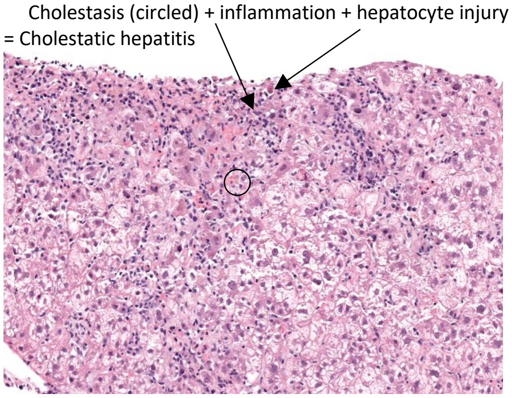
ERCP image courtesy of Dr. Alexander Towbin, @CincykidsRad; used with permission


Ductular cholestasis

Link

SEPSIS

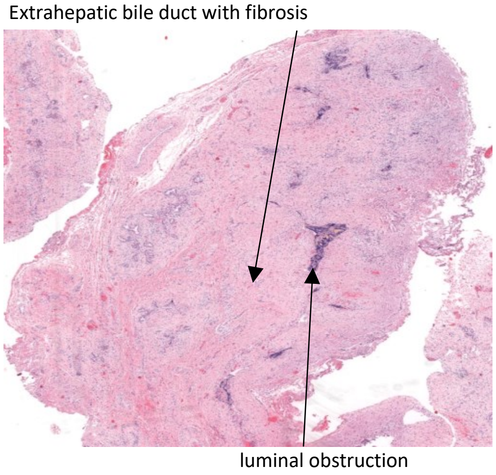
- Characteristic feature- **Ductular cholestasis ("cholangitis lenta")**
- Ductular reaction with inspissated bile and flattened, atrophic epithelium
- This pattern is not specific to sepsis; clinical context is critical
- Affects **systemically ill patients with sepsis, bacteremia, or jaundice**


Cholestasis (circled) + inflammation + hepatocyte injury
= Cholestatic hepatitis

DRUG REACTION

- Most common histologic pattern of drug-induced liver injury is cholestasis
- **Bland/pure cholestasis:** Cholestasis with minimal inflammation
- **Cholestatic hepatitis:** Cholestasis with inflammation and hepatocellular injury
- **Prolonged cholestasis/ductopenia:** Greater than three months
- **Sclerosing duct injury:** Fibrosis affecting large bile ducts (similar to PSC)
- Drugs and patterns of injury can be found at http://livertox.nih.gov/

Path Presenter Link


Extrahepatic bile duct with fibrosis
luminal obstruction

Path Presenter

BILIARY ATRESIA

MORPHOLOGY

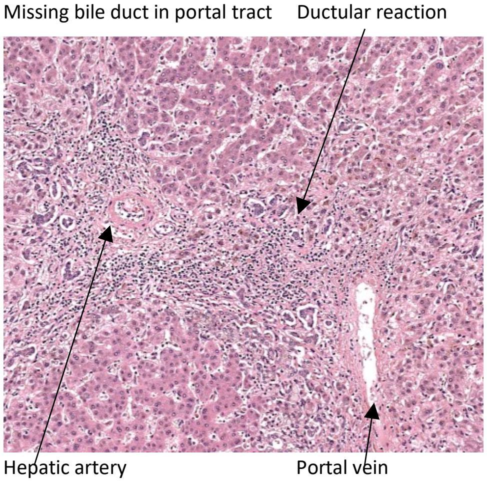
- Large bile duct obstruction type findings in liver biopsies: non-specific requires clinical and radiographic correlation
- Affects extrahepatic ducts with fibrosis and luminal obstruction

OTHER HIGH YIELD POINTS

- Idiopathic **prenatal destruction/fibrosis of extrahepatic bile ducts**
- **Most common cause of pathologic infant jaundice**
- Usually present in the first few weeks of life with jaundice and failure to thrive; 10% have mutation in ***Jagged1* gene**
- Hepatobiliary (HIDA) scan demonstrates the failure of excretion of radiotracer into the duodenum
- **Surgical intervention with Kasai procedure and/or liver transplantation required**

DIFFERENTIAL DIAGNOSIS

- Bile salt deficiencies (previously called Progressive Familial Intrahepatic Cholestasis (PFIC)) and inherent defects in bilirubin metabolism


Missing bile duct in portal tract
Ductular reaction
Hepatic artery
Portal vein

NEONATAL PAUCITY OF INTRAHEPATIC BILE DUCTS

MORPHOLOGY

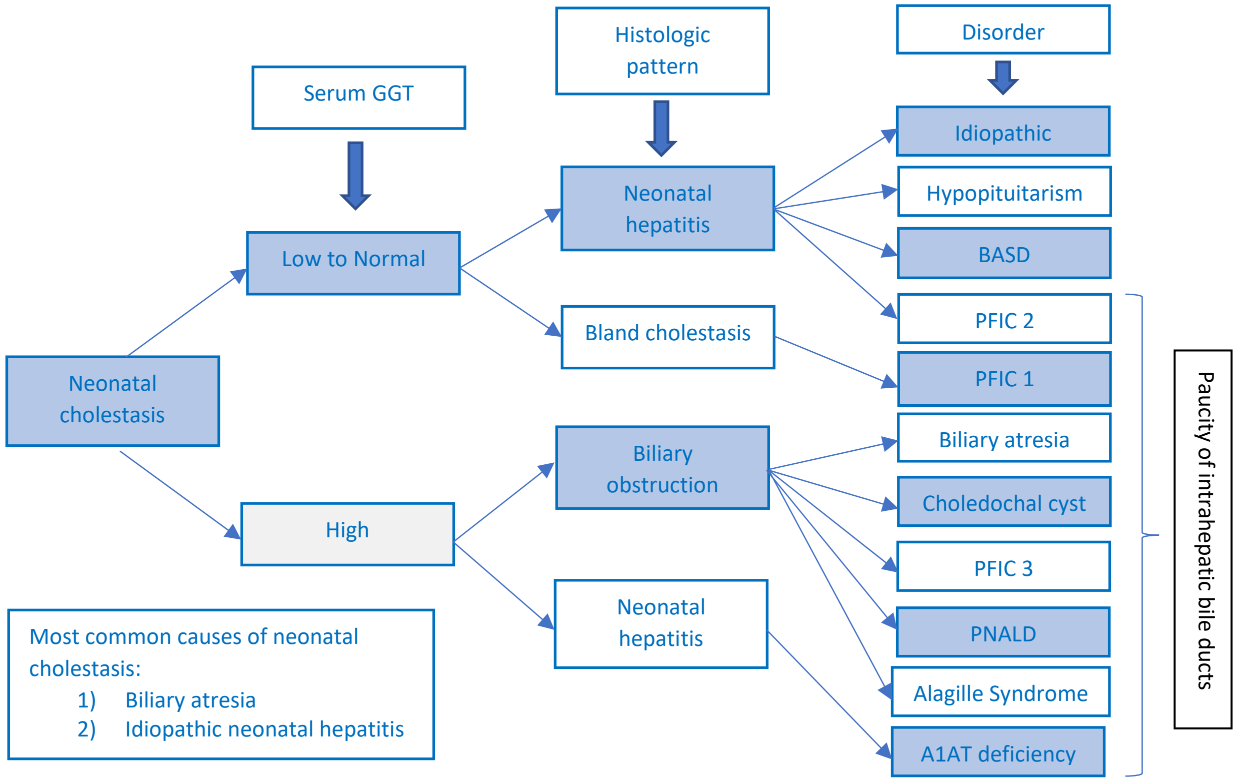
- **Absence of >50% of the bile ducts in portal tracts**
- Ductular reaction and cholestasis may be present
- Eventually can lead to cirrhosis
- CK7 can be helpful in assessment of missing bile ducts
- Increased copper in periportal hepatocytes

OTHER HIGH YIELD POINTS

- Can be **syndromic or non-syndromic**
- In non-syndromic cases, bile duct loss is present at birth
- Syndromic: **Alagille syndrome** due to ***JAG1/NOTCH2* mutations; associated with cardiac and skeletal abnormalities**

Path Presenter

NEONATAL CHOLESTASIS DIAGNOSTIC ALGORITHM

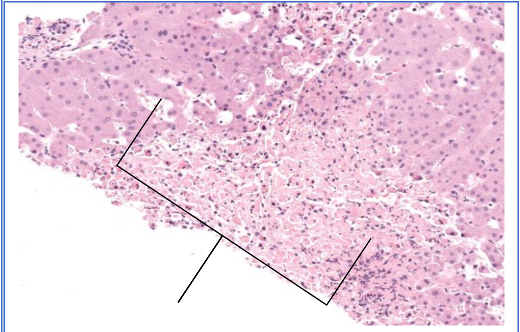

Serum GGT
Histologic pattern
Disorder
Neonatal cholestasis
Low to Normal
High
Neonatal hepatitis
Bland cholestasis
Biliary obstruction
Neonatal hepatitis
Idiopathic
Hypopituitarism
BASD
PFIC 2
PFIC 1
Biliary atresia
Choledochal cyst
PFIC 3
PNALD
Alagille Syndrome
A1AT deficiency
Paucity of intrahepatic bile ducts

Most common causes of neonatal cholestasis:

1) Biliary atresia
2) Idiopathic neonatal hepatitis

BASD- Bile Acid Synthetic Defect, PFIC- Progressive Familial Intrahepatic Cholestasis, PNALD- Parenteral Nutrition-Associated Liver Disease

VASCULAR PROCESSES



Centrizonal coagulative necrosis

SHOCK LIVER

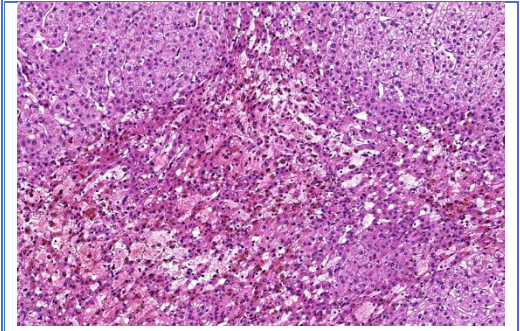
MORPHOLOGY

- **Central (zone 3) coagulative necrosis** without inflammation
- Collapse of reticulin plate

OTHER HIGH YIELD POINTS

- Pattern is seen with **liver hypoperfusion** of any cause
- Massive elevation in AST and ALT (usually in the 1000s)
- Differential diagnosis: **Acetaminophen (Tylenol) toxicity**

Path Presenter



SINUSOIDAL OBSTRUCTION SYNDROME

MORPHOLOGY

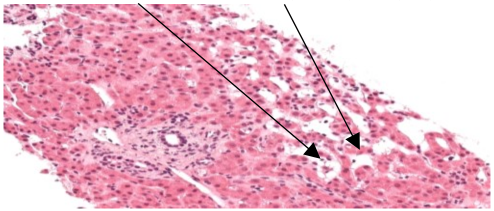
- **Central vein obliteration** by fibrosis (best seen on the trichrome stain)
- Also see sinusoidal dilatation, congestion, and endothelial edema

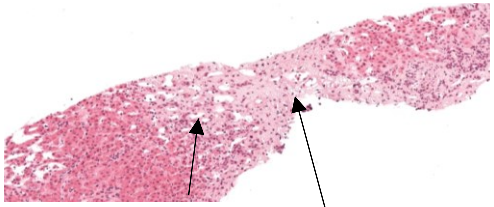
OTHER HIGH YIELD POINTS

- **Due to injury to sinusoidal endothelium**
- Etiology: **Chemotherapy or stem cell transplantation**

Figure: Sinusoidal dilatation in sinusoidal obstruction syndrome, image courtesy Dr. Haeryoung Kim, MD.

Sinusoidal dilatation and thinning of hepatocyte plates





VENOUS OUTFLOW OBSTRUCTION

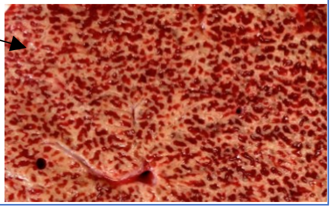
MORPHOLOGY

- Acute cases **show sinusoidal dilatation, congestion, and hepatic plate atrophy**
- **Chronicity causes central vein fibrosis and sinusoidal fibrosis** and can lead to cirrhosis

OTHER HIGH YIELD POINTS

- Common etiologies: **Right-sided heart failure, Budd-Chiari**
- Gross liver appearance: Nutmeg liver

Image courtesy of Dr. Michal Kunc, Poland



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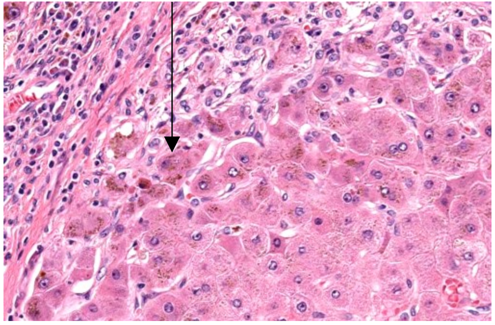
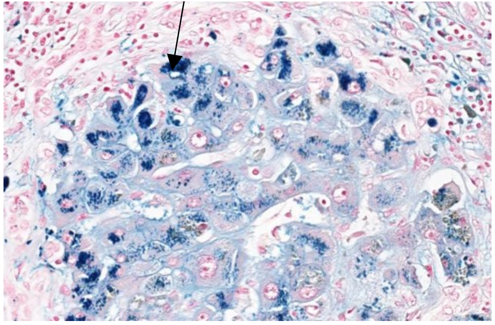
Hemosiderin (brown granules) depostion in hepatocytes



Hepatocellular hemosiderin deposition



HEREDITARY HEMOCHROMATOSIS

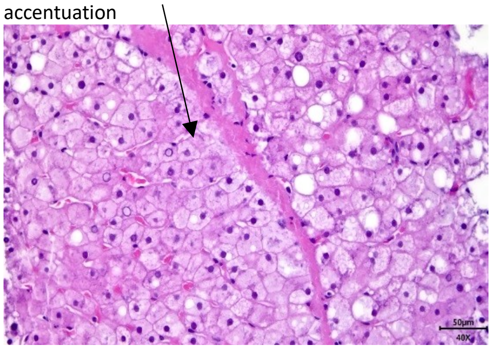
MORPHOLOGY

- Group of inherited disorders of iron metabolism; **Type 1 is due to *HFE* gene mutations** resulting in decreased hepcidin synthesis→ increased iron absorption and storage; **C282Y** is the most common pathogenic allele and accounts for clinically significant iron overload
- **Iron accumulates first within zone 1 (periportal) hepatocytes** with a distinctive pericanalicular pattern and progressively involves all zones
- Iron can also be deposited in the bile duct epithelium and Kupffer cells
- Variable degree of fibrosis and cirrhosis develop over time
- Iron special stain demonstrates iron deposition which is graded semi quantitatively Path Presenter

OTHER HIGH YIELD POINTS

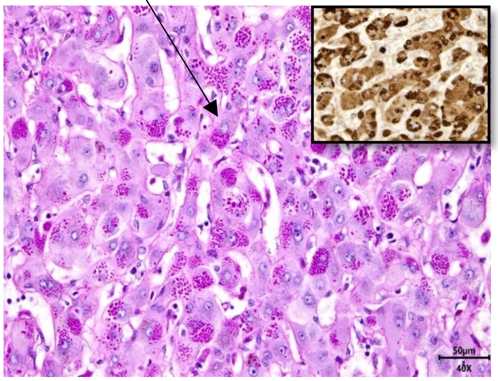
- Genetic testing and hepatic iron quantification tests are other confirmatory methods
- Differential diagnosis includes transfusion and oral supplementation-related iron overload, anemias with ineffective erythropoiesis, chronic liver diseases including alcoholic and nonalcoholic fatty liver diseases, chronic hepatitis C and cirrhosis
- In secondary iron overload: **accumulation predominantly seen in Kupffer cells first,** but substantial hepatocellular deposition occurs when Kupffer cells are saturated

Abundant pale cytoplasm with hepatocyte membrane accentuation



GLYCOGENIC HEPATOPATHY

- Poorly controlled blood sugar levels→ disrupt balance between glycogenesis and glycogenolysis→ abundant glycogen stores →hepatomegaly and elevated LFTs
- Classic clinical setting is **type 1 diabetes mellitus**; also seen in **Mauriac syndrome** (with growth retardation, delayed puberty, cushingoid features and hypercholesterolemia)
- **Diffuse glycogenation of hepatocytes characterized by abundant pale cytoplasm,** often with hepatocyte membrane accentuation; no inflammation; **positive by PAS-D stain** Path Presenter



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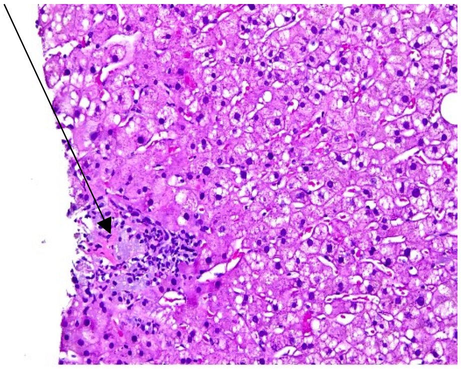
α1-ANTITRYPSIN DEFICIENCY (α1-AT)

MORPHOLOGY

- Autosomal recessive genetic disorder characterized by decreased α1-AT level
- α1-AT gene is codominant with each allele contributing 50% of total protein; **PiM is the normal**/wild-type allele whereas PiS and PiZ are the most common disease-causing alleles; **PiZZ phenotype accounts for most cases with liver disease**
- Histology shows deposition of **eosinophilic, PAS-D positive globules within periportal hepatocytes;** positive by α1-AT IHC
- Neonatal hepatitis features cholestasis and hepatocyte injury (too early for globule formation)

OTHER HIGH YIELD POINTS

- Bimodal clinical presentation: first is neonates and infants with cholestatic liver disease and second is adults with chronic liver disease



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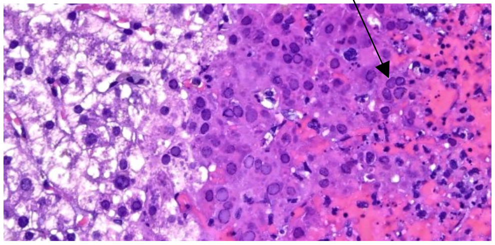
RESOLVING HEPATITIS

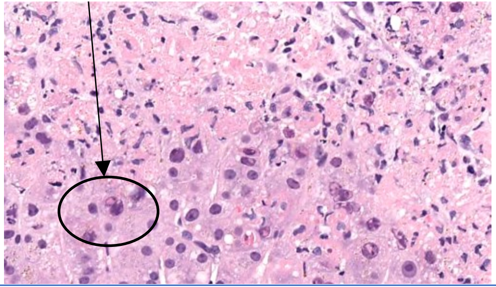
MORPHOLOGY

- **Almost normal appearing liver** with minimal to mild portal inflammation and absent to minimal lobular inflammation
- Mild lobular disarray and lobules often have **scattered clusters of pigmented/ceroid-laden macrophages**
- The Kupffer cell hyperplasia is a clean-up effort in a site of prior injury; Positive with PAS-D stain
- Most common causes are **idiosyncratic drug reaction and acute self-limited viral infections**

OTHER HIGH YIELD POINTS

- Mild cholestasis can also be seen with some drug effects
- Hepatitic injury will resolve after stopping the drug, however liver enzymes may take months to normalize completely





HERPES SIMPLEX VIRUS (HSV) AND ADENOVIRUS INFECTION

MORPHOLOGY

- **Extensive non-zonal hepatocyte necrosis**
- Characteristic intranuclear inclusions are seen adjacent to areas of necrosis
- HSV: Intranuclear inclusions with a rim of marginated chromatin with or without multinucleated hepatocytes
- Adenovirus: Intranuclear inclusions with smudgy nuclear appearance and mild lymphocytic lobular and portal inflammation
- HSV and adenovirus immunohistochemistry confirms the diagnosis

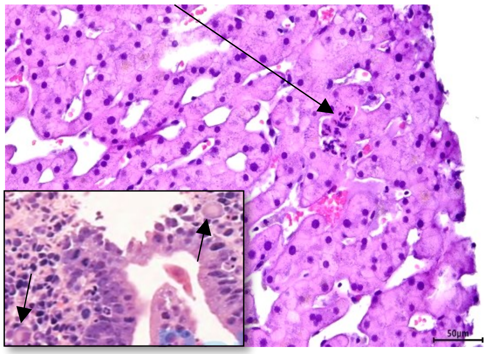
OTHER HIGH YIELD POINTS

- Usually seen in immunocompromised individuals
- Poor prognosis, often fatal

Link Link

Path Presenter

Neutrophilic microabscess in CMV hepatitis



CMV inclusions

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CYTOMEGALOVIRUS (CMV) HEPATITIS

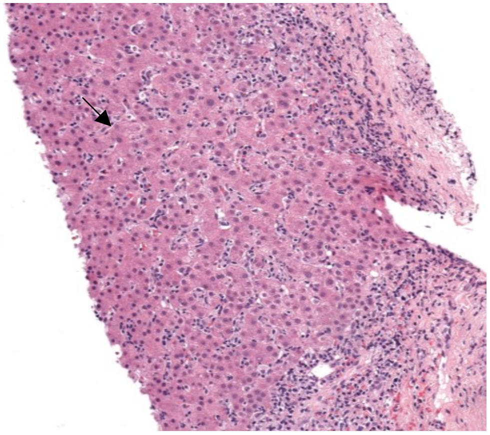
MORPHOLOGY

- Histologic findings are subtle, mild portal or lobular inflammation maybe seen
- Presence of lobular **neutrophilic microabscesses** in some cases is a helpful clue to consider the diagnosis
- Characteristic viral cytopathic effects (nuclear and cytoplasmic enlargement) with viral inclusions when present, can be seen hepatocytes, bile duct epithelium, endothelial cells and Kupffer cells

OTHER HIGH YIELD POINTS

- Typically seen in the setting of immunosuppression, however clinically silent infections can occur in immunocompetent individuals
- Variable clinical presentation (asymptomatic to severe infection) is seen in congenital infection

Activated lymphocytes in sinusoids giving a string of beads appearance



EPSTEIN-BARR VIRUS (EBV) HEPATITIS

MORPHOLOGY

- Often looks like a nondescript hepatitis with mild to moderate portal and lobular inflammation (so often keep in differential diagnosis, especially if young adults or immunocompromised)
- Classically: **lots of activated lymphocytes in sinusoids, giving an appearance of string of beads**
- The degree of hepatocyte injury is usually disproportionately low

OTHER HIGH YIELD POINTS

- Apart from hepatitis, EBV can also cause post-transplant lymphoproliferative disorder (PTLD) and smooth muscle tumors in the liver in immunosuppressed individuals

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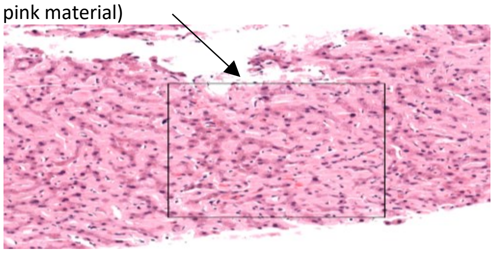
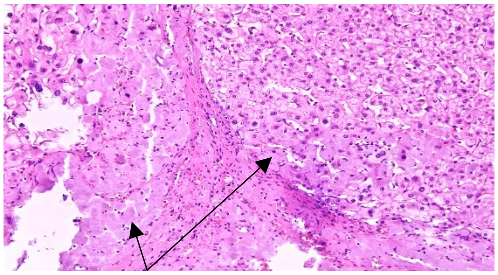
Sinusoidal deposition of amyloid (acellular amorphous pink material)





Globular pattern deposition of LECT2 amyloidosis

AMYLOIDOSIS

MORPHOLOGY

- **Amyloidosis of the liver most frequently occurs secondary to systemic diseases** such as multiple myeloma
- Familial/primary amyloidosis is rare and results from mutations in genes that produce amyloidogenic proteins
- Amyloid deposition appears as amorphous, acellular, eosinophilic deposits in vessels and sinusoids leading to hepatocyte atrophy
- Different types of amyloid seen in the liver including **primary, AL, AA, and Leukocyte chemotactic factor 2 (LECT2) amyloidosis**
- A **distinct globular pattern deposition** is seen in LECT2 amyloidosis (also involves kidney)

OTHER HIGH YIELD POINTS

- **Congo red stain** highlights amyloid as brick-red in bright-field microscopy and demonstrates **apple-green birefringence under polarized light**

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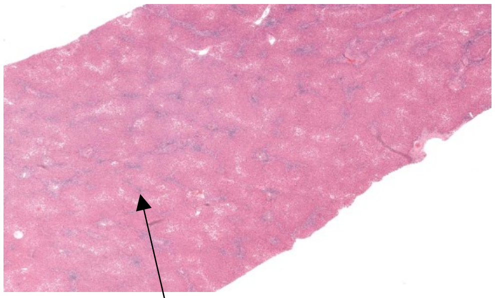
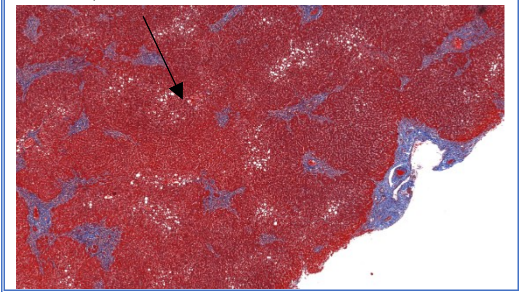
6. LIVER PATHOLOGY



Hyperplastic nodules mimic cirrhosis on low-power; however, trichrome does not confirm cirrhosis



NODULAR REGENERATIVE HYPERPLASIA

MORPHOLOGY

- **Cirrhotic-appearing nodules on gross and radiologic examination; however, histologically no evidence of cirrhosis or fibrosis**
- Results from **changes in hepatic blood flow** from obliteration of small portal veins which leads to localized atrophy→other areas grow to compensate
- Multiple hyperplastic parenchymal nodules (with normal to enlarged hepatocytes) with intervening compressed/atrophied parenchyma
- Findings are best seen on reticulin stain: **Reticulin stain highlights compressed hepatocytes between the nodules**

OTHER HIGH YIELD POINTS

- **Can cause portal hypertension** and mimics cirrhosis

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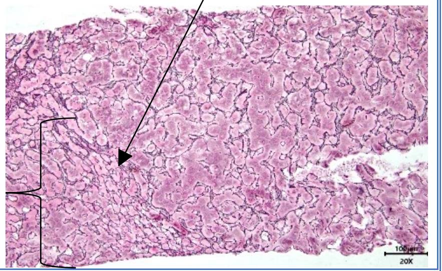
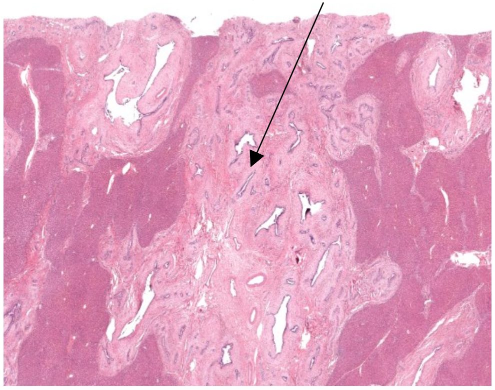


Portal fibrosis with branching abnormal ductal structures



CONGENITAL HEPATIC FIBROSIS

MORPHOLOGY

- Embryologic ductal plate malformation that leads to **bridging fibrosis with prominent malformed ducts**
- Anastomosing irregularly shaped and branching abnormal ductal structures circumferentially arranged around the portal tract
- Varying degrees of portal fibrosis without significant inflammation
- Abnormal/hypoplastic portal veins → leads to portal hypertension

OTHER HIGH YIELD POINTS

- **Associated with autosomal recessive polycystic kidney disease**
- Associated with mutations in ***PKHD1* gene**, that codes for fibrocystin

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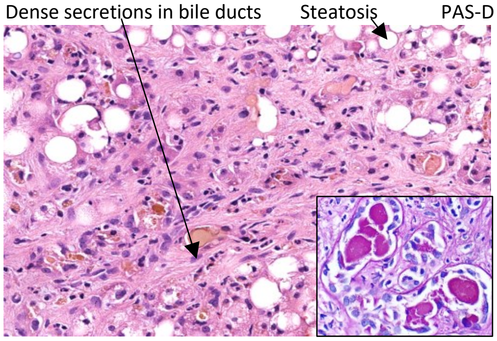
Images courtesy of Dr. Adam L. Booth, @ALBoothMD; used with permission

Dense secretions in bile ducts Steatosis PAS-D



CYSTIC FIBROSIS

- **Autosomal recessive**; mutation in the ***CFTR* gene** results in impaired chloride transport in various organs; **presents with respiratory problems, meconium ileus, or pancreatic insufficiency**
- **Steatosis is the most common finding** in hepatic lobules, however steatohepatitis is uncommon
- **Thick abnormal secretions are present in bile ducts** (similar to lungs and pancreas) → biliary obstruction → epithelial atrophy, bile ductular proliferation, inflammation → fibrosis → biliary cirrhosis
- **Secretions stain with PAS-D**
- Portal hypertension due to obliterative portal venopathy and nodular regenerative hyperplasia

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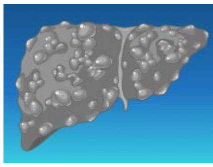
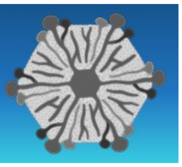


6. LIVER PATHOLOGY



LABORATORY CORRELATION

ACUTE HEPATITIS

Marked transaminitis (AST & ALT >5x normal)

- Non-hepatotropic viruses (CMV, HSV)
- Hepatitis A & E; only acute
- Hepatitis B: Ground glass inclusions
- Autoimmune hepatitis: Plasma cells
- Massive altered hepatic blood flow (such as shock)

CHOLESTATIC HEPATITIS

Elevated Alkaline Phosphatase & GGT; +/- Bili; Jaundice

- Large duct obstruction
- PBC: Female, + AMA, IgM, lymphocytic cholangitis, and florid duct lesion
- PSC: Male, inflammatory bowel disease, concentric fibrosis around ducts; risk of cholangiocarcinoma
- Drug reaction

CHRONIC HEPATITIS

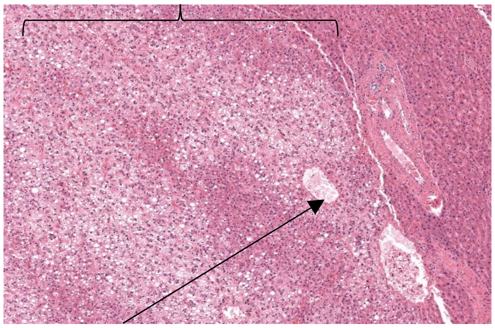
Mild transaminitis (AST & ALT <5x normal)

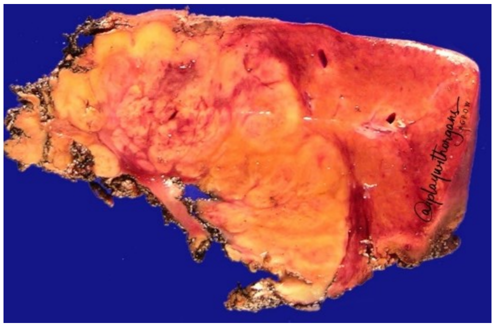
- Hepatitis B: 5% develop chronic hepatitis
- Autoimmune hepatitis: +ANA, ASMA, Elevated IgG: interface necroinflammatory lymphoplasmacytic infiltrate
- Hepatitis C: 80% develop chronic hepatitis; nodular aggregates of lymphocytes
- Hereditary hemochromatosis: +*HFE* gene mutation; elevated transferrin saturation and serum ferritin
- Wilson's disease: Increased liver copper quantitation; mutation in *ATP7B* gene; AST/ALT ratio>2.2; Alkaline Phosph/total bilirubin <4
- A1AT deficiency: PiZZ phenotype; hyaline globules in hepatocytes stain with PAS-D stain
- Alcohol-related: Clinical history of alcohol use: AST:ALT >; more likely to show neutrophils and Mallory's hyaline
- Non-alcoholic steatohepatitis: Diabetes or metabolic syndrome, obesity
- Drug reaction

Based on a presentation by Dr. Max Smith, Mayo Clinic

CIRRHOSIS/ LIVER FAILURE: *Synthetic dysfunction such as elevated INR, low albumin, and low platelets*

LIVER LESIONS: BENIGN





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HEPATOCELLULAR ADENOMA

MORPHOLOGY

- Benign liver neoplasm **associated with use of oral contraceptives/ steroids**
- Composed of benign-appearing hepatocytes with normal plate thickness (1-2 plates) and no cytologic atypia or mitoses
- Key to diagnosis is **absence of true portal tracts; finding of unpaired arteries also helpful**

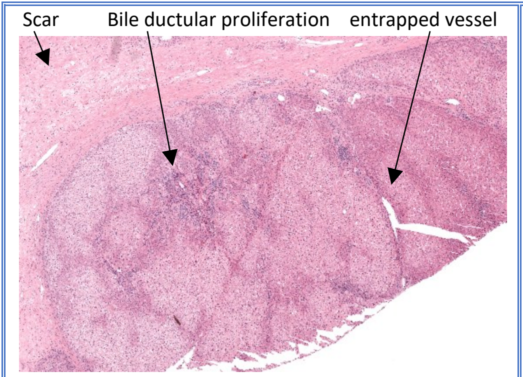
Four subtypes of hepatocellular adenoma

Subtype	Phenotype	IHC
Inflammatory/ Telangiectatic (~45%)	Associated with inflammatory infiltrate, sinusoidal dilatation, bile ductular reaction; transformation to HCC can occur	Positive for Serum Amyloid A (SAA) and CRP
ß-catenin activated (~15%)	May have cellular atypia; **highest risk of malignant transformation**	**Nuclear ß-catenin positive**; diffuse strong glutamine synthetase
HNF1alpha-inactivated (~30%)	Have steatosis; associated with adenomatosis (>10 adenomas); low risk of malignant transformation	Loss of LFABP staining
Unclassified (~10%)	Does not fit other categories	

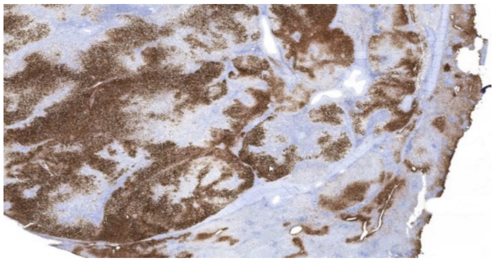
OTHER HIGH YIELD POINTS

- Risk of transformation to hepatocellular carcinoma and or bleeding/rupture

6. LIVER PATHOLOGY



Glutamine Synthetase in FNH: Map-like staining



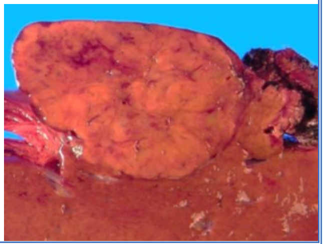
FOCAL NODULAR HYPERPLASIA (FNH)

MORPHOLOGY

- **Regenerative hyperplastic response of hepatocytes due to vascular abnormalities**; not a true neoplasm
- Mimics focal cirrhosis; well-circumscribed with **central stellate scar**, fibrous septa, entrapped vessels, bile ductular reaction, and inflammatory cells
- No true portal tracts
- **“Map-like” staining with glutamine-synthetase**

OTHER HIGH YIELD POINTS

- No association with oral contraceptives; usually asymptomatic
- Most nodules measure < 5 cm
- Most common in young women



Gross image courtesy of Cory Nash, MS, PA (ASCP); used with permission
IHC image courtesy of Dr. Matthew Gosse, @MattGosseMD; used with permission

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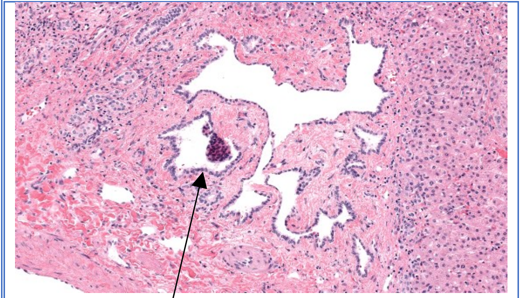


Path Presenter

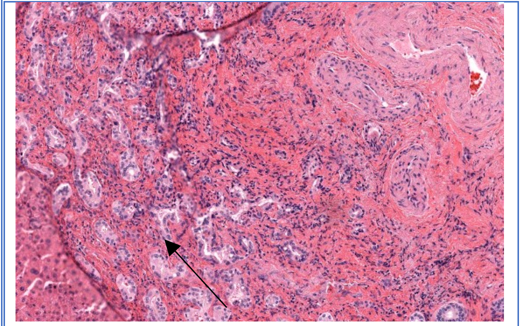
BILE DUCT HAMARTOMA/VON MEYENBURG COMPLEX (VMC)

MORPHOLOGY

- **Benign ductal plate malformation** characterized by **irregular to round dilated bile ducts within fibrous/hyalinized stroma**
- Lumen **may contain bile** or proteinaceous material

OTHER HIGH YIELD POINTS

- Usually **incidental, clinically insignificant, and small (<0.5 cm)**
- If numerous, consideration for ductal malformation-associated diseases such as Caroli disease, Caroli Syndrome, Polycystic kidney disease, and congenital hepatic fibrosis should be given



Proliferation of small uniform ducts with cuboidal cells and round regular nuclei

BILE DUCT ADENOMA AND ADENOFIBROMA

MORPHOLOGY

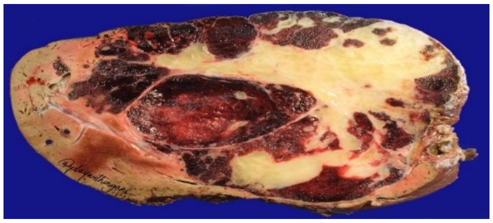
- Bile duct adenoma is a benign lesion characterized by **proliferation of small uniform ducts with cuboidal cells and round regular nuclei**
- Lumen usually **does not contain bile**

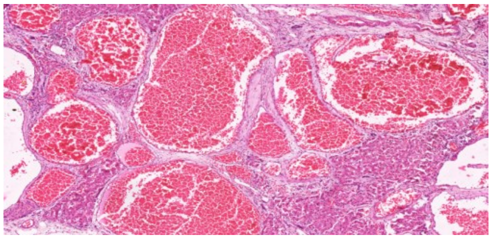
OTHER HIGH YIELD POINTS

- Clinically can be mistaken for metastasis intraoperatively
- Usually <1 cm, subcapsular, and well-circumscribed
- ~50% of bile duct adenomas show ***BRAF*** **V600E mutations**

Path Presenter

6. LIVER PATHOLOGY





Dilated vascular channels lined by endothelial cells

CAVERNOUS HEMANGIOMA

MORPHOLOGY

- Benign vascular lesion composed of dilated vascular channels lined by single layer of flat endothelial cells separated by fibrous septa
- Positive for endothelial markers: ERG, CD31, CD34, FLI1, Factor 8

OTHER HIGH YIELD POINTS

- **Most common benign tumor of the liver**
- Thought to be a malformation and non-neoplastic; diagnosed radiologically
- Often asymptomatic; >5 cm lesions more susceptible to hemorrhage, rupture; they can thrombose and calcify
- More common in females

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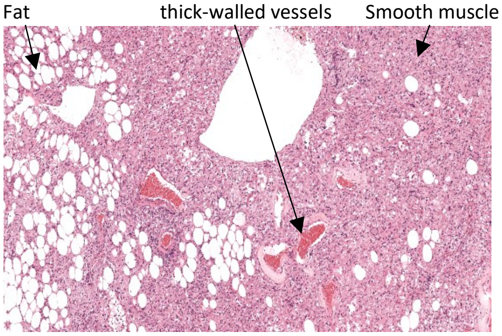
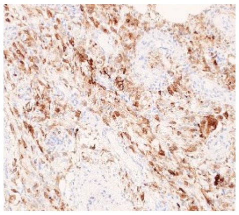
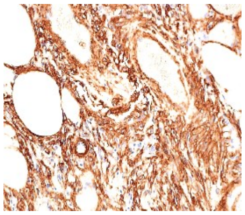
Gross image courtesy of Cory Nash, MS, PA (ASCP); used with permission


Fat
thick-walled vessels
Smooth muscle





ANGIOMYOLIPOMA/PECOMA

MORPHOLOGY

- Mesenchymal tumor, like in the kidney
- Well-circumscribed; consists of variable admixture of fat, smooth muscle, and thick-wall blood vessels
- Smooth muscle may appear epithelioid with eosinophilic cytoplasm; cytologic atypia may be present
- Generally benign, however, very rarely malignant behavior has been reported
- Positive for HMB-45, SMA, Melan-A, and CKIT

OTHER HIGH YIELD POINTS

- Usually, asymptomatic
- F>M; mean age: 56 years
- Usually sporadic but **~5-10% associated with tuberous sclerosis**
- ***TSC1* or *TSC2* mutations**

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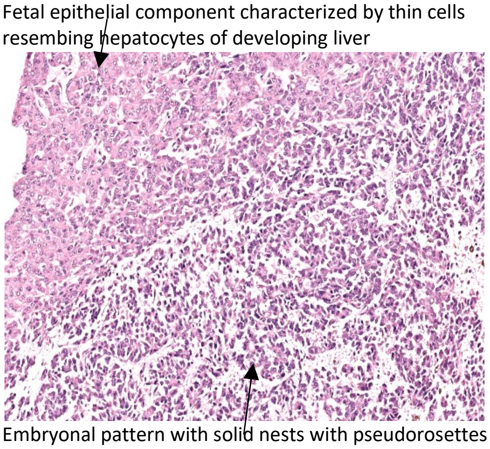
LIVER LESIONS: MALIGNANT


Fetal epithelial component characterized by thin cells resembling hepatocytes of developing liver
Embryonal pattern with solid nests with pseudorosettes

HEPATOBLASTOMA

MORPHOLOGY

- Malignant tumor recapitulating hepatic ontogenesis
- Shows a variety of epithelial (e.g. fetal and embryonal) and mesenchymal cell types ("teratoid")
- **Frequent ß-catenin mutations;** nuclear localization with immunohistochemistry→ worse prognosis

OTHER HIGH YIELD POINTS

- **Most common liver tumor in children**
- Majority of cases between 5 months and 6 years of age
- Majority are sporadic, however some associated with **Beckwith-Wiedemann, familial adenomatous polyposis, or trisomy 18**
- Serum AFP elevated in ~90% cases

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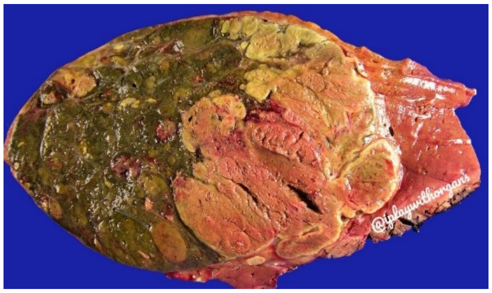
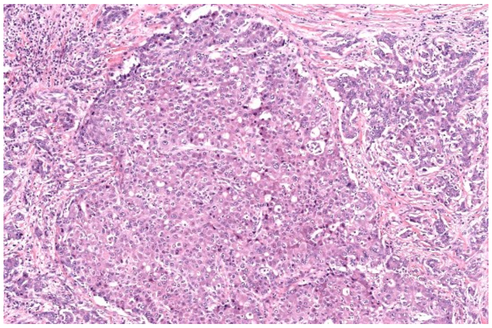
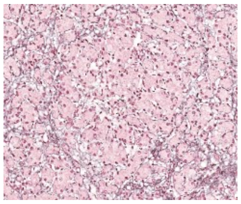


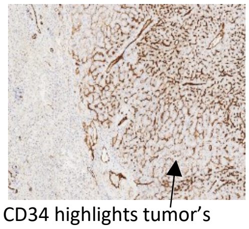
HCC: Green discoloration due to bile production
Image courtesy of Cory Nash, MS, PA (ASCP); used with permission



HCC: Loss of normal trabecular architecture



Reticulin- thickened hepatic plates



CD34 highlights tumor's sinuoidal "capillarization"

HEPATOCELLULAR CARCINOMA (HCC)

MORPHOLOGY

- Malignant tumor of hepatocellular differentiation
- **Widening of hepatocellular plates (>2 cells thick); absent portal tracts and unpaired arterioles**
- Other features include cytologic and architectural atypia such as **pseudoacini/pseudogland formation**
- Stains: **Reticulin highlights widened hepatocyte plates**; CD34 shows sinusoidal **"capillarization;"** positive for Hep-Par1, Arginase, and Glypican-3; glypican-3 is negative in benign liver but positive in moderately-poorly differentiated HCCs

VARIANTS:

- **Fibrolamellar HCC**→ see section below
- **Steatohepatitic HCC** → Associated with hepatitis C and NASH; macrovesicular steatosis, ballooning degeneration, and Mallory's hyaline present; can be difficult to recognize as carcinoma especially on biopsies
- **Macrovesicular-massive HCC** → Thick trabeculae (>10 cells thick) covered by endothelial cells; aggressive subtype with **high AFP, *TP53* mutations or *FGF19* amplification**

OTHER HIGH YIELD POINTS

- HCC often occurs in the setting of cirrhosis (associated with chronic liver injury such as viral hepatitis, alcohol, NASH, hereditary hemochromatosis)
- Usually diagnosed clinically with imaging findings and elevated Alpha Fetoprotein (AFP)
- Treated with resection, embolization, or transplant

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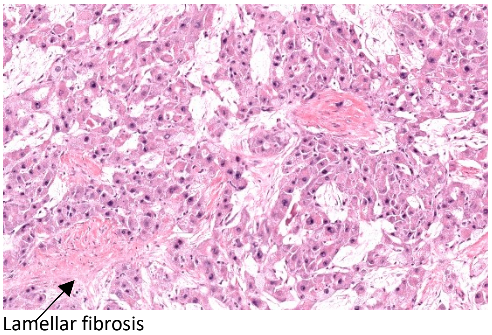
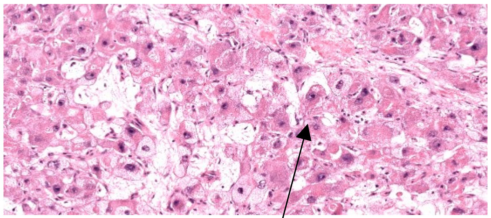


Lamellar fibrosis



Oncocytic tumor cells with prominent nucleoli

FIBROLAMELLAR CARCINOMA

MORPHOLOGY

- **Malignant tumor comprising of large oncocytic cells with prominent nucleoli, lamellar fibrosis, and cytoplasmic pale bodies**
- Positive for CD68 and CK7

OTHER HIGH YIELD POINTS

- Large, solitary tumor; normal AFP
- **Young, non-cirrhotic patients**
- Classically thought to be better prognosis, but this is most likely due to demographics
- Recurrent ***DNAJB1-PRKACA* fusion**

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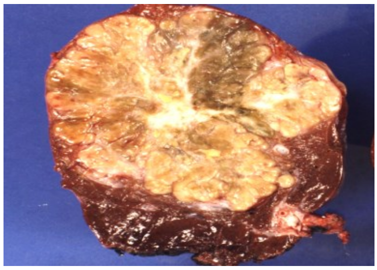
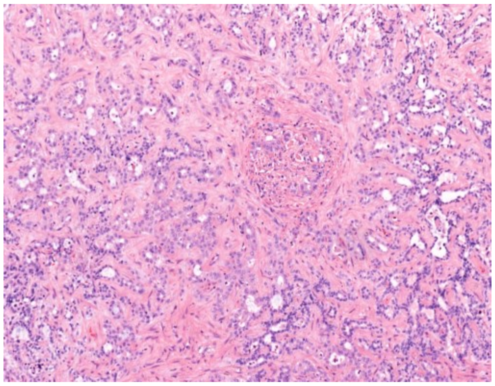
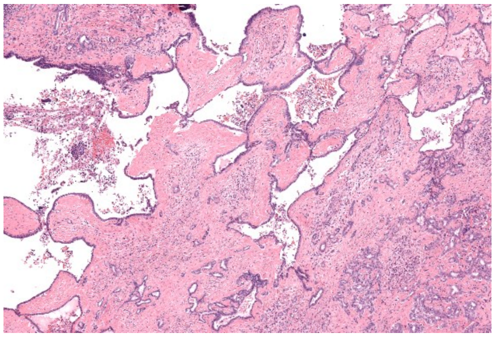


Image courtesy of Dr. Kevin Kuan @kkuanMD; used with permission

Small duct type



Large duct type



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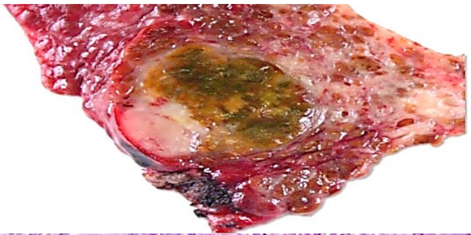
INTRAHEPATIC CHOLANGIOCARCINOMA

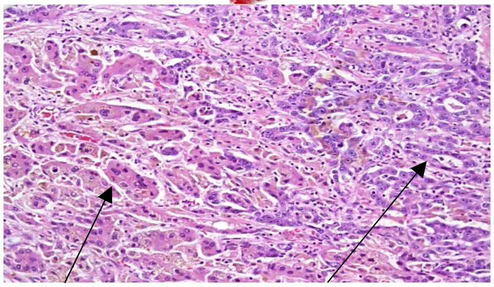
MORPHOLOGY

- **Adenocarcinoma arising in the liver proximal to the left and right hepatic ducts**
- Glands show varying degrees of atypia and differentiation and infiltrate dense fibrous stroma
- **Two variants:**
    - **Small duct type:** Peripheral, large liver masses, risk factors similar to hepatocellular carcinomas
    - **Large duct type:** Hilar, obstructive cholestasis, risk factors similar to extrahepatic bile duct carcinomas (see below); precursors include biliary intraepithelial neoplasia and intratubular papillary neoplasms
- **Growth patterns**: mass-forming, periductal infiltrative, intraductal, and mixed
- Need to exclude metastatic carcinoma
- Non-specific immunoprofile: CK7+ CK20-, CK19+, CEA; Albumin in-situ hybridization supports intrahepatic origin

OTHER HIGH YIELD POINTS

- **Second most common primary malignancy of liver**
- M>F; 55-75 years of age
- Inflammatory disorders such as PSC, liver fluke, Caroli disease, hepatolithiasis, and choledochal cysts can predispose to development of large duct type cholangiocarcinomas
- Intrahepatic tumors show ***IDH*, *EPHA2*, and *BAP1* mutations and *FGFR2* fusions;** different from extrahepatic tumors
- Aggressive carcinomas with poor survival rates





Combined HCC-CCA: Heterogeneous gross appearance
HCC area CCA area

COMBINED HEPATOCELLULAR (HCC)-CHOLANGIOCARCINOMA (CCA)

MORPHOLOGY

- A single tumor with two morphologically distinct areas of hepatocellular carcinoma and cholangiocarcinoma
- HCC areas of heppar1, arginase, and glypican3+ while cholangiocarcinoma areas are CK7+

OTHER HIGH YIELD POINTS

- **Treatment and prognosis are similar to cholangiocarcinoma;** worse prognosis than HCC
- Transarterial chemoembolization (TACE) has been associated with higher frequency of combined tumors
- Mutations of HCC (such as *CTNNB1*) and CCA (such as *KRAS, IDH1*) have been found

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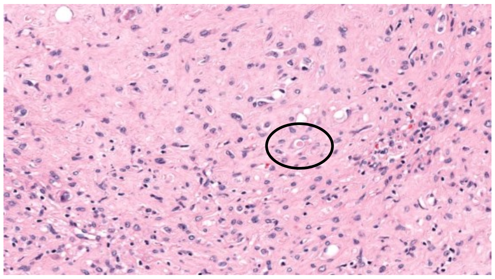
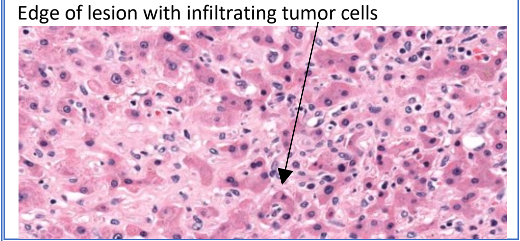
Eosinophilic cells in dense fibrous stroma with signet ring-like features containing RBC (circled)



Edge of lesion with infiltrating tumor cells

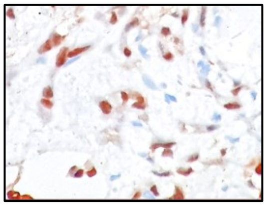


EPITHELIOID HEMANGIOENDOTHELIOMA

MORPHOLOGY

- **Malignant endothelial neoplasm that can be locally aggressive and has metastatic potential**
- Composed of **eosinophilic, slightly epithelioid cells with signet ring-like features representing intracytoplasmic lumina (often containing red blood cells);** associated with dense fibrous stroma
- Can show intravascular papillary growth and infiltrate sinusoidal spaces at the edge of the lesion
- Positive for ERG, CD31, CD34, D2-40, FLI1, CAMTA1, TFE3; keratin positive in ~40%

CAMTA1 IHC



OTHER HIGH YIELD POINTS

- Can affect soft tissue, bone, lung, skin, and liver
- ***WWTR1-CAMTA1*** or ***YAP1-TFE3*** **fusion**

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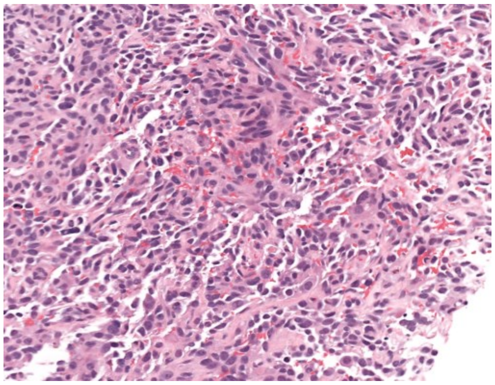

Epithelioid to spindled malignant cells associated with vessels/red blood cells

ANGIOSARCOMA

MORPHOLOGY

- Malignant endothelial tumor; **most common liver sarcoma**
- Spindled to epithelioid tumor cells, variably atypical, with mitoses and anastomosing spaces; tumor cells grow along pre-existing vascular spaces; usually large and **multifocal**
- Positive for vascular markers: CD31, CD34, ERG, D2-40; keratins positive in up to 35% of cases

OTHER HIGH YIELD POINTS

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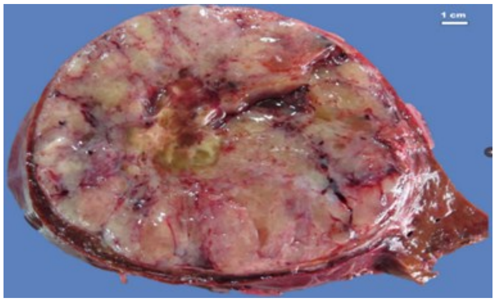
- M>F; presents at >50 years of age
- **Associated with exposure to vinyl chloride, thorotrast, and androgen steroids**
- Poor prognosis



Images courtesy of Dr. Raul Perret, @kells108; used with permission

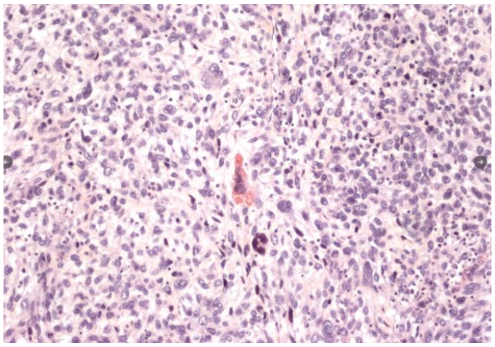
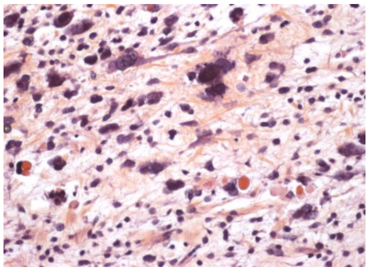
UNDIFFERENTIATED EMBRYONAL SARCOMA

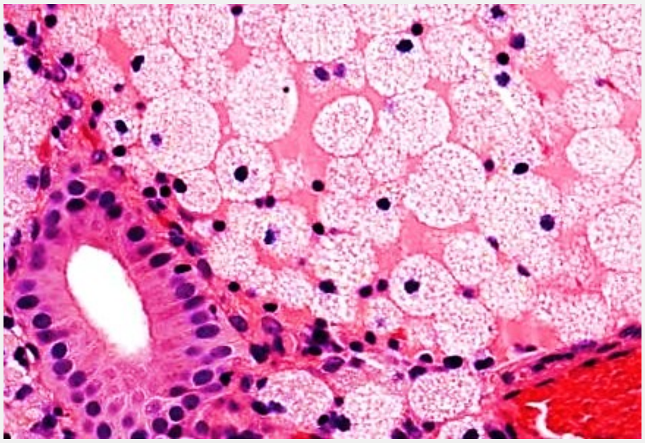
MORPHOLOGY

- Variably cellular tumor with spindled, oval, and pleomorphic/anaplastic cells with hyaline globules
- Stroma can show myxoid changes
- Hyaline globules are PAS-D positive; high Ki-67

OTHER HIGH YIELD POINTS

- Large tumors, 10-30 cm
- Well-demarcated, solitary, with cystic, gelatinous, and hemorrhagic foci
- 9-15% of pediatric hepatic tumors; usually present 6-10 years
- Presents with abdominal pain, fever, and normal AFP levels
- Often associated with mesenchymal hamartoma; thus also called mesenchymal sarcoma
- Treatment usually involves complete resection and chemotherapy

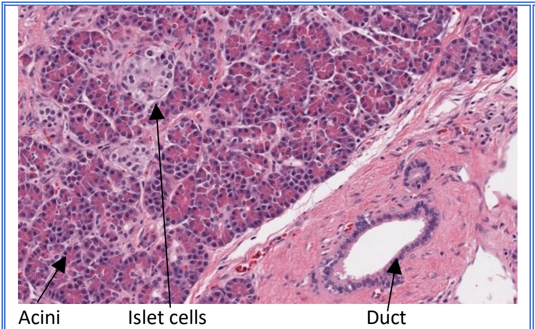
 Spindled, oval, and pleomorphic/anaplastic cells	- Cases show *MALAT1* gene rearrangement: t (11:19) and mutations in *TP53* Path Presenter 


Cholesterol polyp, Gall Bladder (H&E stain). Image courtesy: Akanksha Gupta, MD

CHAPTER 7: PANCREATOBILIARY PATHOLOGY

Manju Ambelil, MD
Snehal Sonawane, MD
Akanksha Gupta, MD

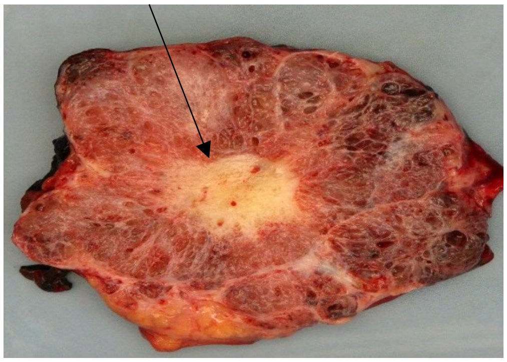
7. PANCREATOBILIARY PATHOLOGY



PANCREAS NORMAL HISTOLOGY

- **Lobular** architecture with two glandular components, and the duct system
- Exocrine glands: Composed of **secretory acini**
- Acinus contains columnar to pyramidal cells with a granular appearance
- Endocrine glands/islets of Langerhans: Composed of **4 major cell types**
- Beta cells, alpha cells, delta cells, and pancreatic polypeptide cells
- Fine duct channels drain acini and converge into the main duct system
- **Small ducts** lined by **flattened to cuboidal** epithelium and **large ducts** lined by **simple columnar** epithelium
- Lobules are separated by connective tissue containing vessels and nerves

Central stellate scar



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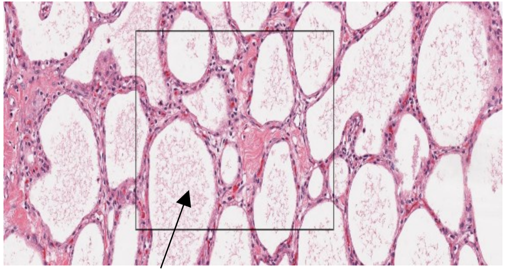


Multiloculated cysts

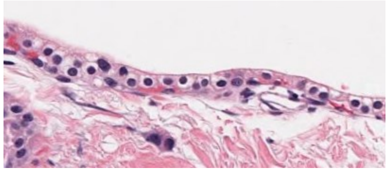
SERous CYSTADENOMA

MORPHOLOGY

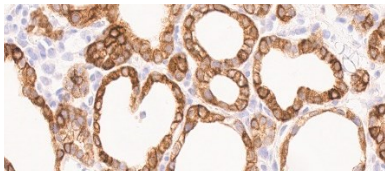
- Gross: Multilocular, sponge-like, or **honeycomb** appearance with a central **stellate fibrous scar**
- Microscopy: Cysts lined by a single layer of cells with defined cell borders
- Composed of bland, uniform, **cuboidal** cells with **clear, glycogen-rich cytoplasm** and **small round nuclei**
- Glycogen→ stains with **PAS** (and digested by diastase)
- IHC: Positive for **inhibin, Cytokeratin, GLUT-1, and MUC6**

OTHER HIGH YIELD POINTS

- F: M ratio 3:1
- Associated with von Hippel Lindau Syndrome **(VHL)**
- Most are **benign with excellent prognosis** and rare incidence of metastasizes→ Serous cystadenocarcinoma



Uniform cuboidal cells with clear cytoplasm



Inhibin

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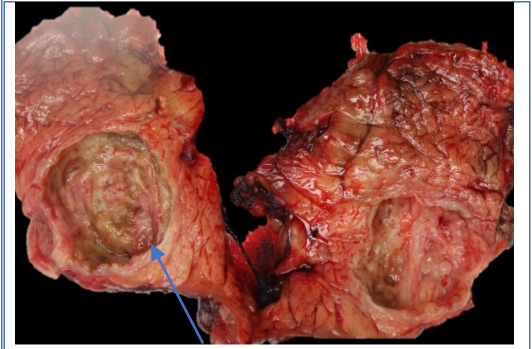
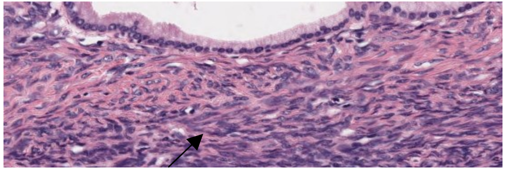


Cyst with fibrous capsule © Upasana Joneja



Ovarian type subepithelial stroma © Upasana Joneja

MUCINOUS CYSTIC NEOPLASM (MCN)

MORPHOLOGY

- Gross: **Multilocular** cyst surrounded by a **thick fibrotic capsule**
- Microscopy: Cyst-forming, mucin-producing neoplasm with a distinct **ovarian-type subepithelial stroma** in the wall
- The lining epithelium is predominantly columnar, mucinous epithelium
- Ovarian stroma: densely packed spindled cells
- IHC: **Ovarian** stroma stains- **ER, PR, Inhibin, and Smooth muscle actin**; Lining **epithelium stains- cytokeratin, CEA and MUC5AC**

OTHER HIGH YIELD POINTS

- Almost exclusively in **women**
- Typically located in the **pancreatic body or tail**
- **Does not** connect to the ductal system (unlike IPMN)
- Must be **thoroughly sampled** to exclude invasive component
- **KRAS** mutations are more common
- Other mutations identified include ***TP53* and *SMAD4***

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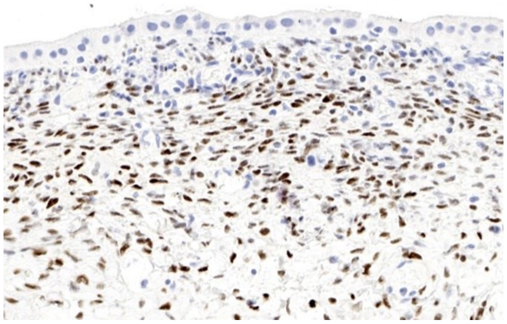
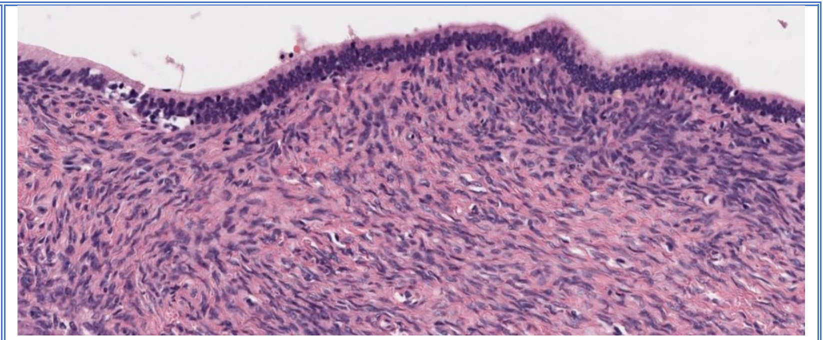
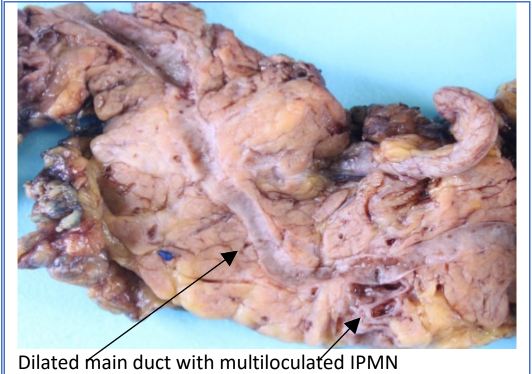
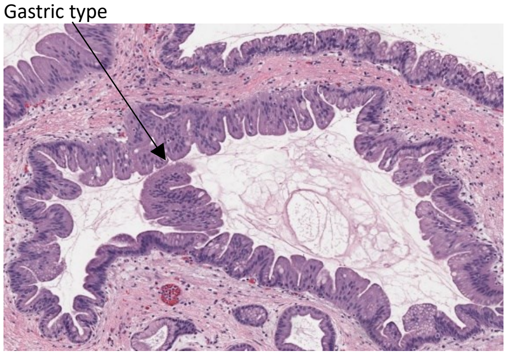

ER Positive

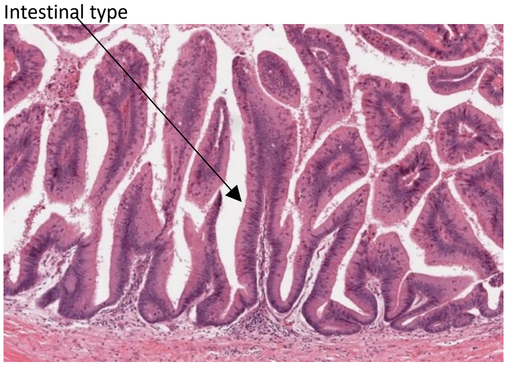

Ovarian type stroma


Dilated main duct with multiloculated IPMN
Credit: Upasana Joneja @Ujoneja

Gastric type



Intestinal type



INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

MORPHOLOGY

- Grossly visible (typically >5 mm) intraductal proliferation of mucinous epithelial cells
- Most often in the **head** of the pancreas, but multi-centric or the entire ductal system involvement are possible
- Lesions can involve the main pancreatic duct (main-duct IPMN), branches (branch-duct IPMN), or mixed duct types.
- Microscopy: **Dilated ducts lined with mucinous epithelium**
- Flat or variable number of papillae are seen, and **no ovarian-type stroma**
- 3 Subtypes
  - ➢ **Gastric type:** Most common, resembles foveolar cells, usually with low-grade dysplasia and branch-duct involvement
  - ➢ **Intestinal type:** Long papillae, tall, columnar epithelium, usually with low- or high-grade dysplasia and main-duct involvement
  - ➢ **Pancreatobiliary type:** Complex branching papillae, resembles biliary epithelium, low cuboidal with amphophilic cytoplasm, usually with high-grade dysplasia and main-duct involvement
- IHC: Positive ductal markers: **CK7, CK 19, CEA, CA19-9**. Mucin glycoprotein (MUC) expression and CDX2 are useful to distinguish the subtypes
- Gastric type: MUC5AC+, MUC6±
- Intestinal type: MUC2+, CK20+, CDX2+, MUC5AC+
- Pancreatobiliary type: MUC1+, MUC5AC+, MUC6+

OTHER HIGH YIELD POINTS

- **KRAS** mutations are the most common. **GNAS** mutations are also common and seem to be relatively unique to **IPMNs**
- **RNF43** is the next common mutation seen
- **TP53 and SMAD4** mutations are seen in those with **invasive** carcinoma
- Invasive carcinoma arising in IPMNs is of two types: tubular or colloid type
- **Tubular** carcinomas are similar to pancreatic ductal adenocarcinomas (PDAC) and usually arise in **pancreatobiliary-type** IPMNs
- **Colloid** carcinomas are associated with **intestinal-type** IPMNs and have a better prognosis than PDAC
- Invasive focus of **<5 mm** has a better prognosis

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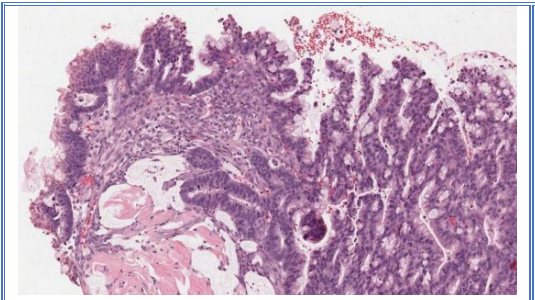
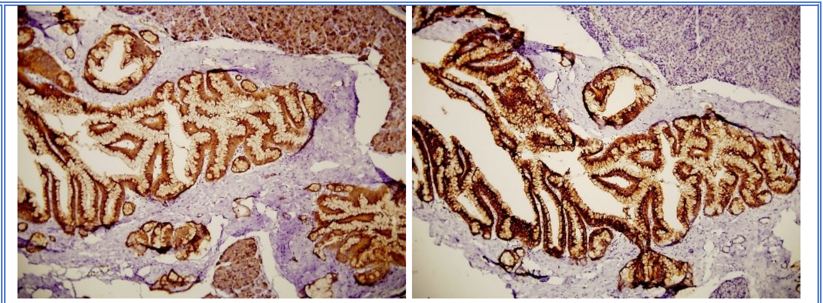
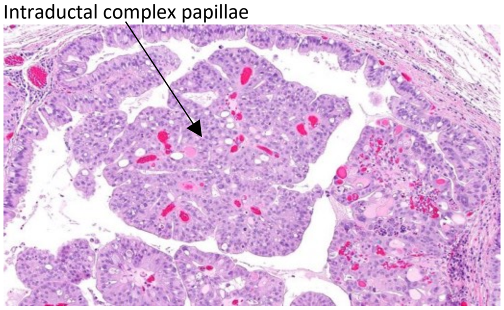


Pancreatobiliary type with high-grade dysplasia

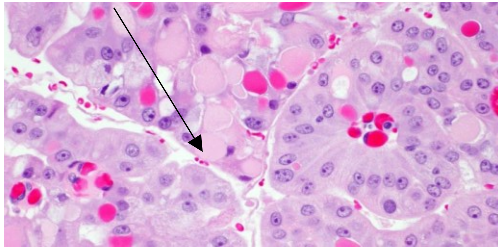


MUC-2 and MUC-5AC Courtesy: Michele Angelo, MD (@BellaMicheleang)

Intraductal complex papillae



Eosinophilic cytoplasm & round nuclei



Courtesy: Dr. Olca Basturk, MD (@OlcaBasturk)

INTRADUCTAL ONCOCYTIC PAPILLARY NEOPLASM (IOPN)

MORPHOLOGY

- Gross: Cystic dilation of ducts with friable red-tan papillary or nodular projections
- Microscopy: Intraductal **complex arborizing** papillary growth pattern, lined by **2-5 layers of cuboidal cells**
- Cells have abundant eosinophilic cytoplasm and round, uniform nuclei with a prominent nucleolus
- Intraepithelial lumina imparts **cribriform** architecture
- IHC: **MUC6+, Hep Par1+, MUC1+**

OTHER HIGH YIELD POINTS

- Unlike IPMNs, IOPNs **lack KRAS, GNAS, and RNF4** mutations
- A subset of IOPNs harbors **DNAJB1-PRKACA** fusions, the same fusion as in fibrolamellar HCC
- Most exhibits high-grade dysplasia and invasive carcinoma occurs in 30% of IOPNs
- **Indolent** behavior, even with invasive carcinoma

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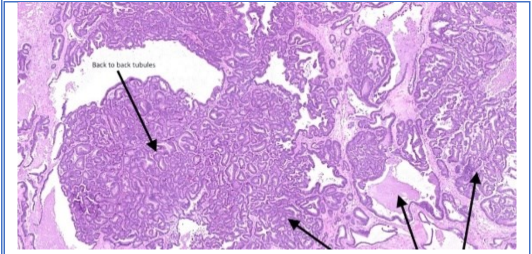
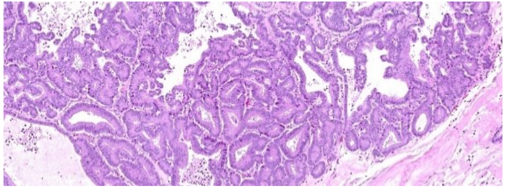
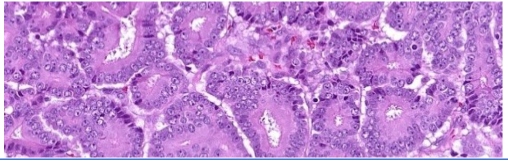


Back-to-back tubules Growth as multiple nodules



cuboidal or columnar cells © Monica Vyas, MD



INTRADUCTAL TUBULOPAPILLARY NEOPLASM (ITPN)

MORPHOLOGY

- Gross: **Nodular solid** masses within dilated ducts; cystic change is less evident
- Microscopy: Intraductal epithelial neoplasm that features predominantly **back-to-back tubules**, resulting in a **cribriform** architecture, and lined by cuboidal or columnar cells
- Can have **focal papillary** growth, and there is no overt mucin production
- Often have **high-grade dysplasia, brisk mitotic** activity, and **necrosis**
- IHC: **CK7+, CK19+, MUC1+,** and variable MUC6; MUC2 and MUC5AC (a marker of all types of IPMNs) are negative

OTHER HIGH YIELD POINTS

- Unlike IPMNs, ITPNs **lack KRAS and GNAS** mutations
- May show **PIK3CA** mutation
- Invasive carcinomas are of **tubular** type and characterized by irregular infiltrating glands associated with desmoplastic stromal reaction
- Overall **prognosis better than ductal adenocarcinoma**

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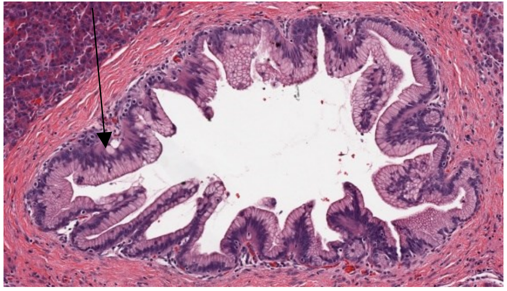
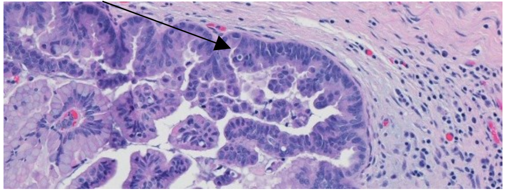
7. PANCREATOBILIARY PATHOLOGY

Low-grade PanIN



High-grade PanIN (loss of nuclear polarity)



PANCREATIC INTRAEPITHELIAL NEOPLASIA (PanIN)

MORPHOLOGY

- Non-invasive, non-mass forming pancreatic ductal epithelial neoplasm, usually < 5 mm in diameter
- Microscopy: Low-grade and high-grade PanIN
- **Low-grade PanIN:** Flat or papillary mucin-producing epithelium, basally located or pseudostratified nuclei with mild to moderate cytologic atypia
- **High-grade PanIN** (Carcinoma in situ): Severe cytologic atypia **with loss of nuclear polarity** and often **abnormal architecture** (papillary, micropapillary, or cribriform)

OTHER HIGH YIELD POINTS

- High-grade PanIN is the main **precursor** to ductal adenocarcinoma
- **KRAS** mutations (seen in >90% of PanIN) and **telomere shortening** are early molecular changes, and ***p16* (*CDKN2A*)** mutations seen in **high-grade PanIN**

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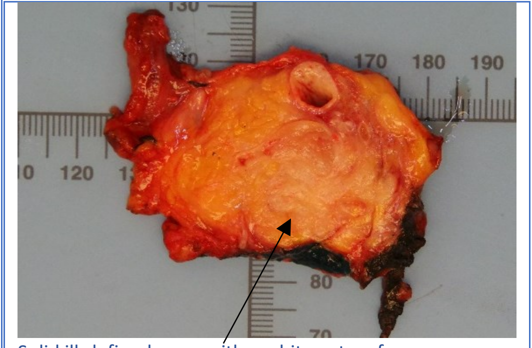
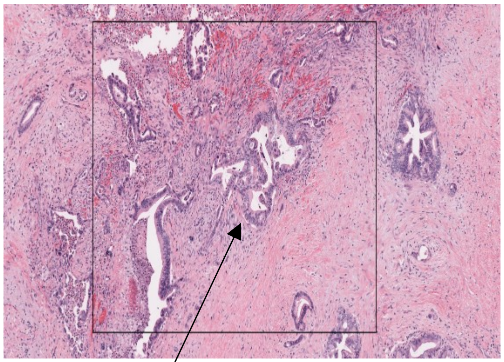
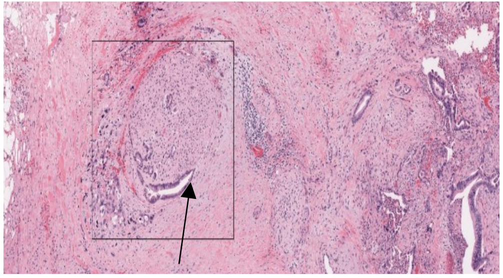


Solid ill-defined mass with a white cut surface



Infiltrating glands surrounded by desmoplastic stroma

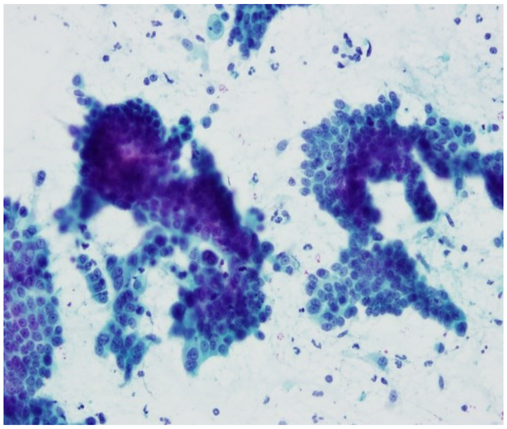


Perineural invasion

PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

MORPHOLOGY

- Gross: Solid, firm, poorly defined masses with infiltrative borders, common in the head of the pancreas
- Microscopy: Differentiation varies from well to moderately to poorly differentiated, showing haphazardly infiltrating duct-like glandular structures that elicit an **abundant desmoplastic** response
- Cells usually contain mucin, and clear cell changes are common; variable nuclear pleomorphism (3-4 times the size of non-neoplastic nuclei) and several histologic subtypes are there
- **Adenosquamous carcinoma:** Glandular and squamous differentiation, the **squamous** component should account for ≥ **30%** of the tumor; worse prognosis than conventional PDAC
- **Colloid carcinoma**: ≥ **80%** of the neoplastic epithelium suspended in extracellular mucin, most arise in association with intestinal-type IPMN; better prognosis than conventional PDAC
- **Hepatoid carcinoma:** ≥ **50%** of tumor displays histologic and immunohistochemical evidence of hepatocellular differentiation
- **Medullary carcinoma**: Poorly differentiated, syncytial growth with abundant tumor-infiltrating lymphocytes, often microsatellite-instable; **better** prognosis than conventional PDAC
- **Invasive micropapillary carcinoma**: ≥ **50%** of tumors show small solid nests of cells suspended within stromal lacunae; aggressive behavior
- **Signet-ring cell (poorly cohesive) carcinoma**: At least **80%** of the tumor consists of individual poorly cohesive cells
- **Undifferentiated carcinoma with osteoclast-like giant cells**: contains three cell types- neoplastic mononuclear cells, non-neoplastic osteoclast-like multinucleated giant cells, and a mononuclear histiocytic component
- **Undifferentiated carcinoma**: diffuse growth pattern without overt glandular differentiation and three morphologic patterns are there
  - **Anaplastic** undifferentiated: At least 80% tumor with solid sheets of bizarre cells
  - **Sarcomatoid** undifferentiated: At least 80% of the tumor with spindle cells ± heterologous elements, loss of INI 1 is seen



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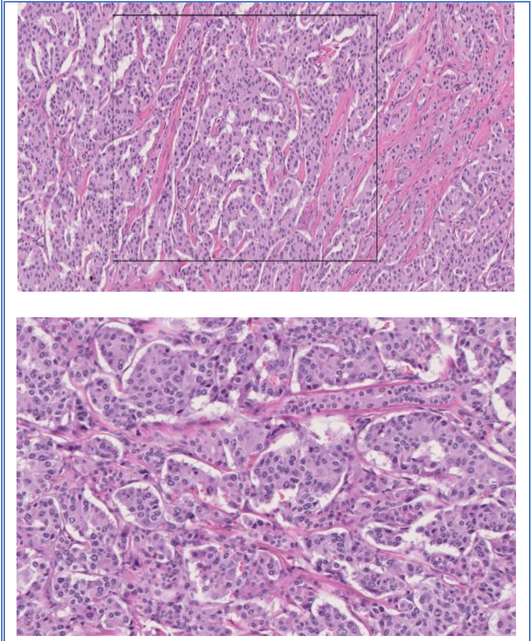
  - **Carcinosarcoma**: Sarcomatoid and epithelial elements each constitute at least 30% of the neoplasm
- IHC: **CK7, CK8, CK18, CK19, and MUC1** are usually positive.
- **Loss of nuclear expression of SMAD4/DPC4 and p16** in half of the tumors
- **Altered p53** expression (overexpression or null) in 75-80% of tumors

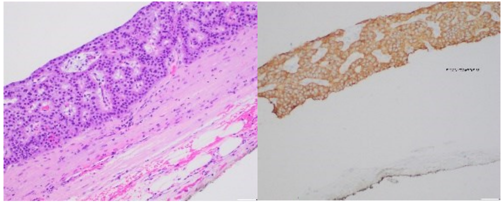
OTHER HIGH YIELD POINTS

- Most common mutations include **KRAS, TP53, CDKN2A, and SMAD4 (DPC4)**
- Precursor lesions: IPMN, MCN, and PanIN
- Perineural and lymphovascular invasions are common
- T stage is based on **tumor size** and independent of any extrapancreatic tumor extension
- **Poor prognosis**, depends on the stage

Path Presenter



Well-differentiated NET, trabeculae of uniform cells
Credit: Elizabeth Montgomery, MD (@LizMontgomery)



Well-differentiated NET Synaptophysin
Credit: Upasana Joneja @Ujoneja

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PANCREATIC NEUROENDOCRINE NEOPLASMS

MORPHOLOGY

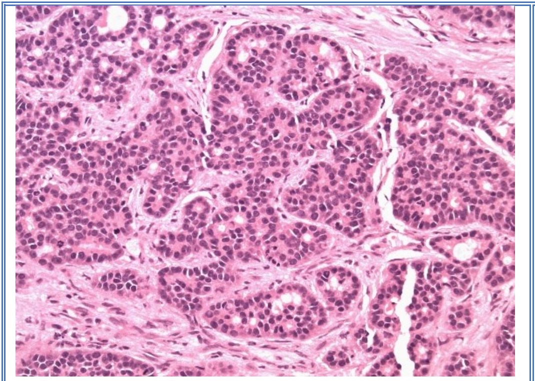
- Includes neuroendocrine tumors (**PanNET**) and neuroendocrine carcinomas (**PanNEC**).
  - PanNE**T**: **Well-**differentiated and graded as **G1, G2, and G3**
  - PanNE**C**: **Poorly** differentiated and **high-grade** neoplasms
- Gross: **Solid well-circumscribed** mass, but cystic changes can be prominent
- Microadenoma: PanNET <0.5 cm in size
- Microscopy: Well-differentiated NET- Various architectural patterns like trabeculae, gyri, solid nests, rosettes, or gland-like; composed of uniform cuboidal cells with round nuclei and coarsely stippled (**salt and pepper**) chromatin
- Poorly differentiated NEC: Sheet-like growth; 2 types- small cell and large cell NECs
- Small cell NEC: **scant** cytoplasm, finely granular chromatin, nuclear **molding, abundant mitotic** rate, and foci of punctate to geographic **necrosis.**
- Large cell NEC: moderate to **abundant** cytoplasm, large nuclei with **prominent nucleoli**, and increased mitotic activity
- IHC: **Synaptophysin, Chromogranin, INSM1**

OTHER HIGH YIELD POINTS

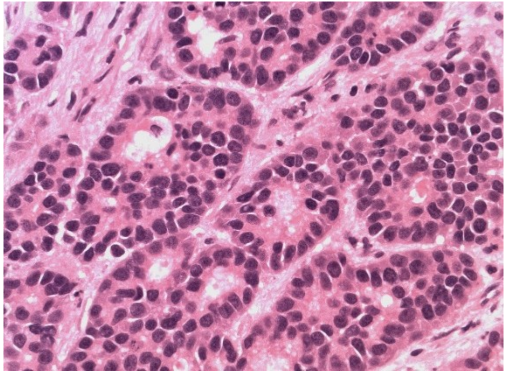
- Well-differentiated NET: associated with ***MEN1, VHL, NF-1,* and *DAXX/ATRX*** mutations
  - Malignant but slow-growing, indolent progression.
  - **Mitotic rate and/or Ki-67** labeling index are required for accurate grading of NET
- Functioning NETs include: Glucagonoma, Gastrinoma, Insulinoma, Somatostatinoma, VIPoma
- Poorly differentiated NEC: ***TP53* and *RB1*** mutation are common, rapidly growing aggressive malignancy, mitotic rate typically **>20 per 2mm^{2},** and Ki-67 labeling index ranges from **50-95%**

NET Grade (G)	Mitotic rate (per 2mm^2)	Ki-67 index (%)
G1	<2	<3
G2	2-20	3-20
G3	>20	>20

7. PANCREATOBILIARY PATHOLOGY



Nested growth, Courtesy: Runjan Chetty @RunjanChetty



Path Presenter

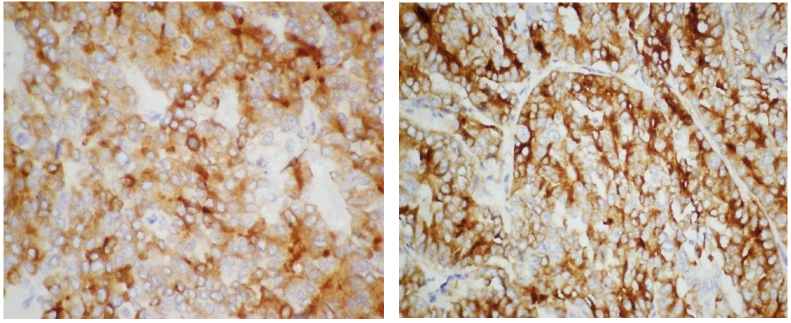
ACINAR CELL CARCINOMA

MORPHOLOGY

- Gross: **Solid well-circumscribed** mass occasionally with necrosis or cystic change
- Microscopy: **Highly cellular**, lacks desmoplastic stromal response, with acinar, solid, trabecular, or nested growth pattern
- Cells have moderate amounts of **granular eosinophilic** cytoplasm (with or without **zymogen** granules), uniform nuclei with a single prominent nucleolus, and the **mitotic** rate is usually high
- It **can be mixed** with neuroendocrine or ductal carcinomas
- IHC: **Trypsin, chymotrypsin, BCL10** (highly specific and sensitive), lipase, or amylase, and cytokeratins (CK7, CK19)

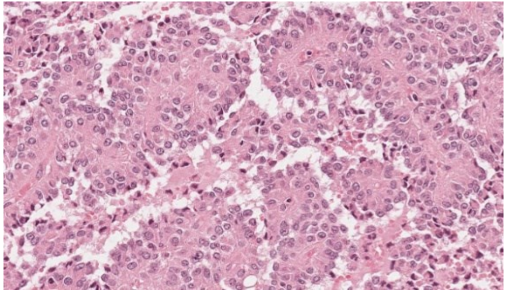
OTHER HIGH YIELD POINTS

- Predominantly in **elderly men**
- Unlike PDAC, acinar cell carcinoma **lacks KRAS, CDKN2A, TP53, and SMAD4 mutations**
- Poor prognosis (better than PDAC, but less than Pancreatic NET)

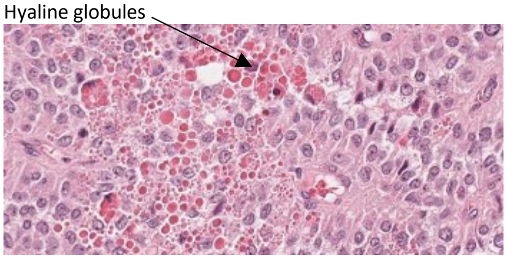


BCL10 and Trypsin. Courtesy: Anthony J Gill (@CaDxPath)

Pseudopapillary architecture



Hyaline globules



Credit: Elizabeth Montgomery, MD (@LizMontgomery)

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SOLID PSEUDOPAPILLARY NEOPLASM

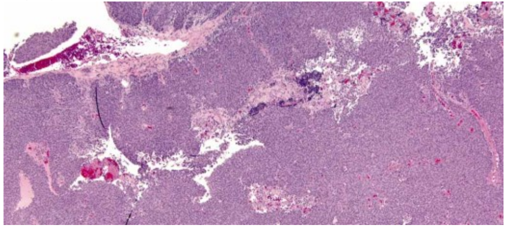
MORPHOLOGY

- Gross: **Well-circumscribed solid** tumors with variable size, hemorrhagic necrosis, and pseudocystic changes in larger masses
- Microscopy: **Solid and pseudopapillary** structures admixed with hemorrhage and necrosis
- Solid tumor **resembles a neuroendocrine** tumor, composed of monomorphic, poorly cohesive cells
- Pseudopapillae are formed when cells detach from fibrovascular cores
- Tumor cells with eosinophilic or vacuolated cytoplasm often contain **PASD+ hyaline globules**, round to oval, often **grooved or intended** nuclei
- Cholesterol clefts, foamy histiocytes, and calcifications may occur in the stroma
- IHC: **Nuclear β-catenin+, loss of E-cadherin**, also positive for cyclin D1, CD56, CD10, PR, CD99 (dot-like), sometimes express CK or CD117 or synaptophysin; however, **negative for chromogranin and acinar markers (trypsin)**

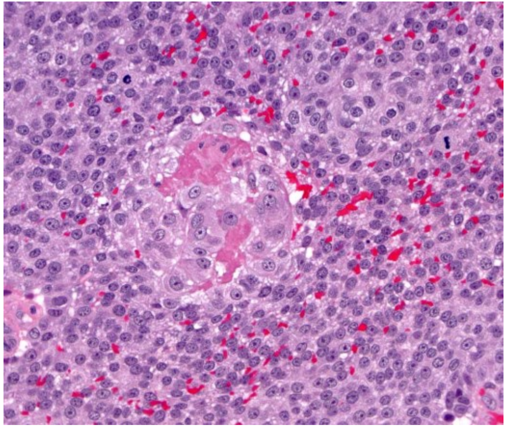
OTHER HIGH YIELD POINTS

- Occur predominantly in **adolescent girls and young women** with a slight preference for the pancreas **tail region**
- Somatic mutations in **CTNNB1 (encoding β-catenin)**
- **Excellent prognosis**: metastatic behavior cannot be predicted by perineural invasion, angioinvasion, and deep infiltration to surrounding structures

Highly cellular lobules separated by fibrous bands



Squamoid nests



Courtesy: Miguel Reyes-Mugica (@mreyesm)

PANCREATOBLASTOMA

MORPHOLOGY

- Gross: **Solitary well-circumscribed solid lobulated mass**
- Microscopy: **Highly cellular lobules** with an acinar, solid, or trabecular pattern, separated by **fibrous bands**
- Most of the tumor looks like acinar cell carcinoma, a focal neuroendocrine component may be present, but **defining component** for establishing the diagnosis is **squamoid nests**
- Acinar differentiation shows cells polarized around small lumina with modest nuclear atypia and a single prominent nucleolus
- Squamoid nests are composed of epithelioid to spindle cells with eosinophilic/ clear cytoplasm arranged in whorls; may show keratinization
- IHC: **Acinar** component stains with trypsin, chymotrypsin, BCL10; synaptophysin, chromogranin positive in **neuroendocrine** component and **squamoid nests** stain with EMA and often nuclear β-catenin.

OTHER HIGH YIELD POINTS

- Most frequent pancreatic neoplasm in **childhood**
- Most are sporadic, but there is an association with **Beckwith-Wiedemann** and **Familial adenomatosis polyposis** syndrome
- Usually **indolent, curable** tumors with a favorable outcome in children than in adults, but worse prognosis with metastatic and non-resectable tumors

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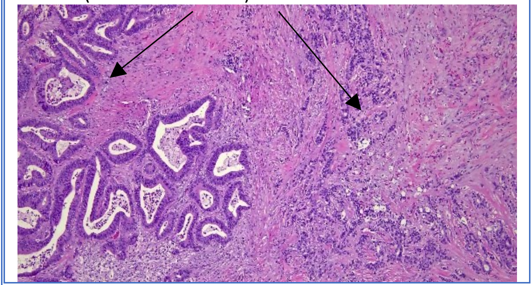
MiNEN (Mixed ductal-NET)



MIXED NEUROENDOCRINE NON-NEUROENDOCRINE NEOPLASM (MiNEN)

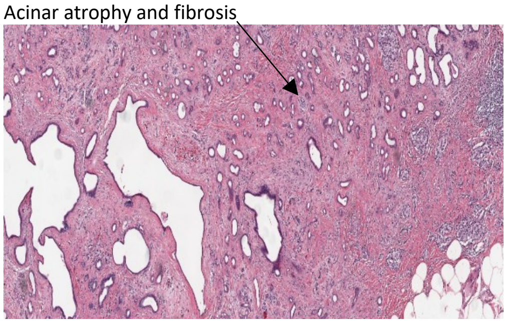
MORPHOLOGY

- Neoplasms composed of morphologically recognizable neuroendocrine and non-neuroendocrine components; **each comprises ≥ 30%** of tumor volume
- Gross: **Solid** tumors with focal necrosis
- Microscopy: Mixed ductal-NEC, mixed ductal-NET, mixed acinar-NEC, and mixed acinar-ductal-NEC are seen

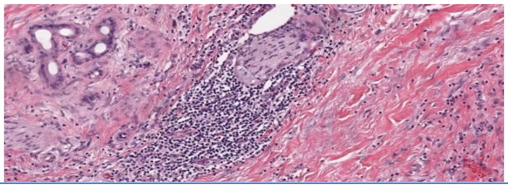
OTHER HIGH YIELD POINTS

- A **monoclonal** origin for **both** components of the tumor
- Usually, metastasize to lymph nodes and liver

Acinar atrophy and fibrosis



Foci of chronic inflammation



CHRONIC PANCREATITIS

MORPHOLOGY

- Gross: Diffuse **fibrosis** and induration, **cysts** of varying sizes, and calculi may be seen
- Microscopy: Varying degrees of **acinar atrophy**, **fibrosis**, and **ductal distortion** are the hallmark features
- Foci of **chronic inflammation** are seen but lesser than that in autoimmune pancreatitis
- **Pseudohypertrophic** appearance of islets due to loss of acinar tissue

OTHER HIGH YIELD POINTS

- The most common cause is **alcohol**
- **Groove (paraduodenal) pancreatitis** is a distinct form centered around the minor papilla and affects the duodenal wall and paraduodenal pancreatic tissue in the form of fibrosis and cystic changes
- Helpful features to distinguish from pancreatic ductal adenocarcinoma include
  - ➢ **Retained lobular** architecture

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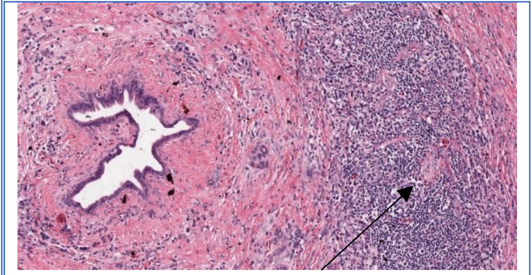
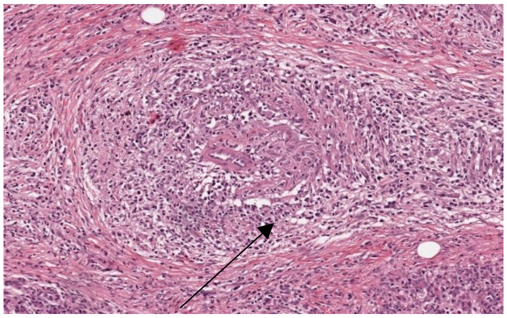
- Absence of **cytologic** features of malignancy (nuclear size variation >4:1, nuclear membrane irregularities, pale vacuolated cytoplasm)
- Lack of single-cell infiltration, perineural invasion, and association of glands with arteries
- Retained SMAD4 and lack of aberrant p53 expression


Storifirm fibrosis and Inflammation around the ducts


Fibrosis & obliterative phlebitis

AUTOIMMUNE PANCREATITIS (AIP)

MORPHOLOGY

- Gross: **firm pancreas**, occasionally mass forming and mimicking carcinoma
- Microscopy: two variants are there, type 1 and 2, both demonstrate **dense chronic inflammation centered around the ducts along with fibrosis**
- **Type 1**(**IgG4-related** pancreatitis or lymphoplasmacytic sclerosing pancreatitis): hallmark features of dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis
- **Type 1 AIP** can also have scattered eosinophilic infiltrates, lymphoid aggregates, and increased **IgG4+** plasma cells (>10/HPF in biopsies and >50/HPF in resection specimens, both with an **IgG4/IgG ratio of >40%)**
- **Type 2 AIP**: periductal lymphoplasmacytic infiltration, along with granulocytic epithelial lesion (**neutrophilic** infiltration of duct wall), lobular neutrophilic abscesses, fibrosis (not the typical storiform fibrosis as in type 1 AIP), and **absent or rare IgG4+** plasma cells

OTHER HIGH YIELD POINTS

- **Prognosis is good** in both types with steroid therapy

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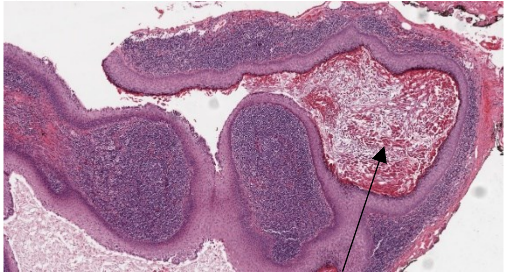
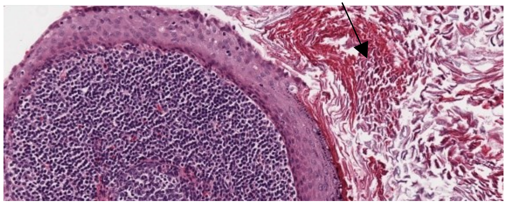
Lymphoepithelial cyst


Keratin debris


Lymphoepithelial cyst wall lined by squamous epithelium and surrounded by reactive lymphoid tissue

NON-NEOPLASTIC CYSTIC LESIONS OF PANCREAS

PSEUDOCYSTS

- Pancreatic or peripancreatic collection of enzyme-rich fluid collection, lacking lining epithelium and wall composed of fibrosis and granulation tissue
- Adjacent pancreas with features of resolving acute or chronic pancreatitis
- Cyst fluid demonstrates **high amylase** (>250 IU/mL) & **low CEA** (<200 IU/mL)

LYMPHOEPITHELIAL CYSTS

- Cyst lined by **squamous** epithelium and surrounded by **reactive lymphoid** tissue
- **Keratinaceous debris** may present within the cyst cavity

ACINAR CYSTIC TRANSFORMATION

- More common in the pancreatic **head,** unilocular or multilocular cysts filled with clear fluid.
- Lined by cells with pale or granular apical cytoplasm and basally oriented nuclei, the lining epithelium exhibit regions of either acinar or ductal differentiation

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HEREDITARY PANCREATITIS

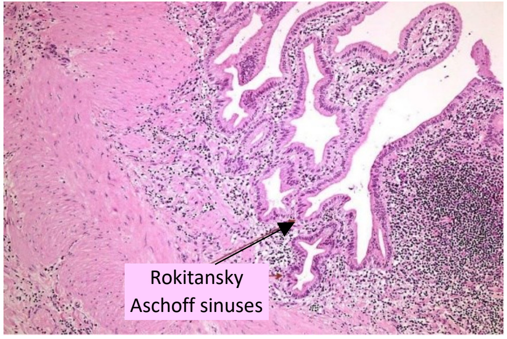
MORPHOLOGY

- **Early childhood** stages with **features similar to acute pancreatitis**, like necrosis and loss of acinar tissue
- **Late adult** stages with **fat replacement** of parenchyma, periductal and interlobular **fibrosis** as in chronic pancreatitis

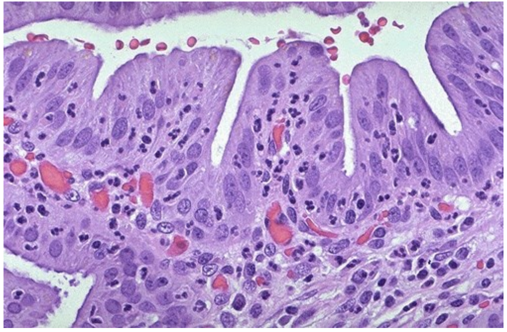
OTHER HIGH YIELD POINTS

- Autosomal dominant disease; is caused by mutations in the **cationic trypsinogen gene** (**PRSS1**); the two most common mutations are **R122H and N29I**
- **High risk** for developing pancreatic carcinoma
- Associated other gene mutations include *SPINK1*, *CFTR,* and *CTRC*

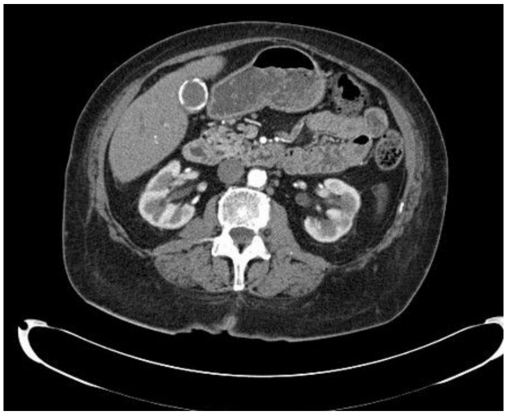
Chronic Cholecystitis



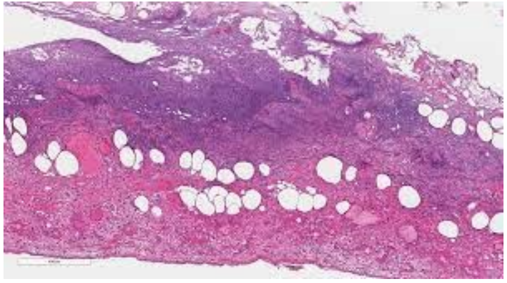
Acute cholecystitis



Porcelain Gall Bladder



Emphysematous Cholecystitis



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GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT

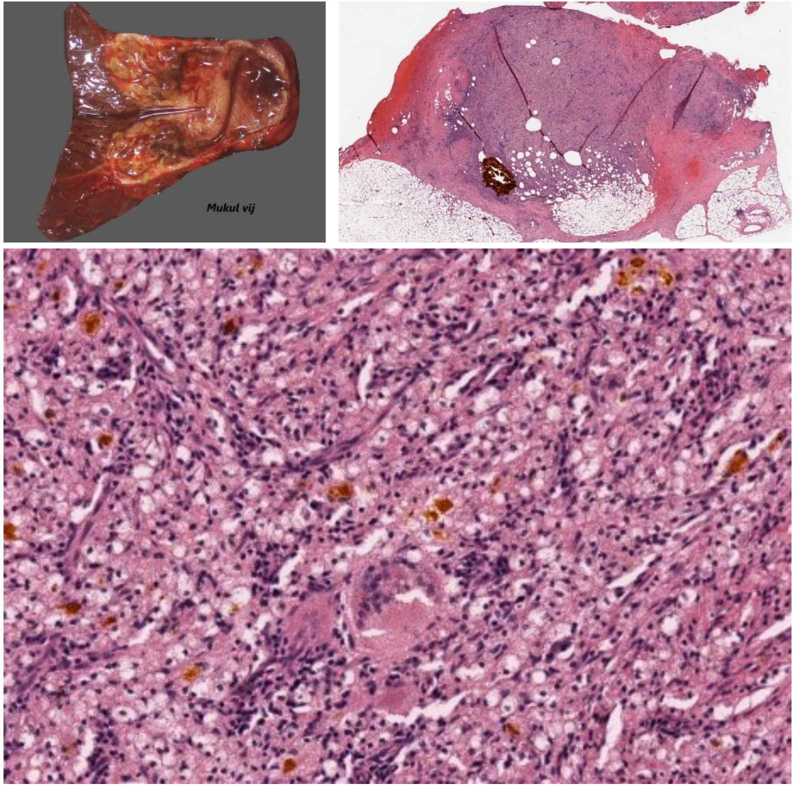
CHOLECYSTITIS

MORPHOLOGY

- Gross: Calculi may be seen in acute and chronic cholecystitis
- Acute cholecystitis feature edema, congestion, and /or necrosis; chronic cholecystitis with **fibrosis** or **even grossly normal** appearing; **xanthogranulomatous** type may resemble carcinoma due to the presence of **firm yellow nodules or plaques**
- Microscopy: Variable picture depending on the clinical duration- acute neutrophilic inflammation with hemorrhage, necrosis, or gangrenous change in the acute phase; chronic phase- mononuclear inflammatory infiltrate, fibrosis, metaplastic changes, and **Rokitansky-Aschoff** sinuses (herniation of mucosa into or through muscularis)

OTHER HIGH YIELD POINTS

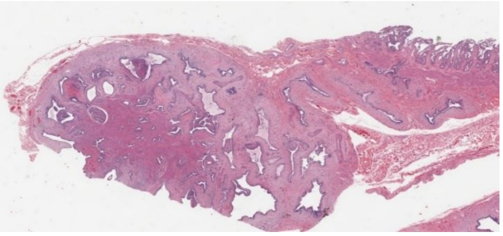
- Variants: **Xanthogranulomatous cholecystitis**- chronic inflammatory infiltrate composed of lipid-laden macrophages, lymphocytes, plasma cells, eosinophils, and neutrophils, admixed with fibrosis, cholesterol clefts, and giant cells, often produce mural or extramural nodule
- **Porcelain gallbladder**- diffuse dystrophic calcification with fibrosis; associated with a high risk of carcinoma
- **Emphysematous cholecystitis**- a variant of acute cholecystitis caused by gas-producing bacteria, particularly clostridial organisms



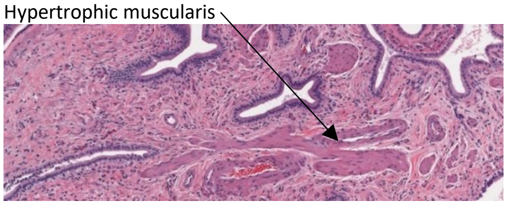
Xanthogranulomatous cholecystitis:
Characteristic yellowish wall thickening and ulceration Credit: Mukul Vij MD @vij_mukul
Microscopy: - lipid-laden macrophages with bile pigment, chronic inflammatory infiltrate, and giant cells, often producing mural or extramural nodule (low magnification image).

7. PANCREATOBILIARY PATHOLOGY

Cystically dilated glands



Hypertrophic muscularis



ADENOMYOMA/ADENOMYOMATOUS HYPERPLASIA

MORPHOLOGY

- Gross: Firm white nodular area usually in the **fundus** (adenomyoma- if solitary), but can also be a diffuse process
- Microscopy: **Cystically dilated benign biliary glands** along with **hypertrophic muscularis and fibrosis**

OTHER HIGH YIELD POINTS

- Other hyperplastic and metaplastic changes include hyperplastic polyps/mucosal hyperplasia (pedunculated or sessile), inflammatory polyps, pyloric metaplasia, intestinal metaplasia, and squamous metaplasia
- Among this pyloric gland metaplasia is a common finding associated with chronic injuries

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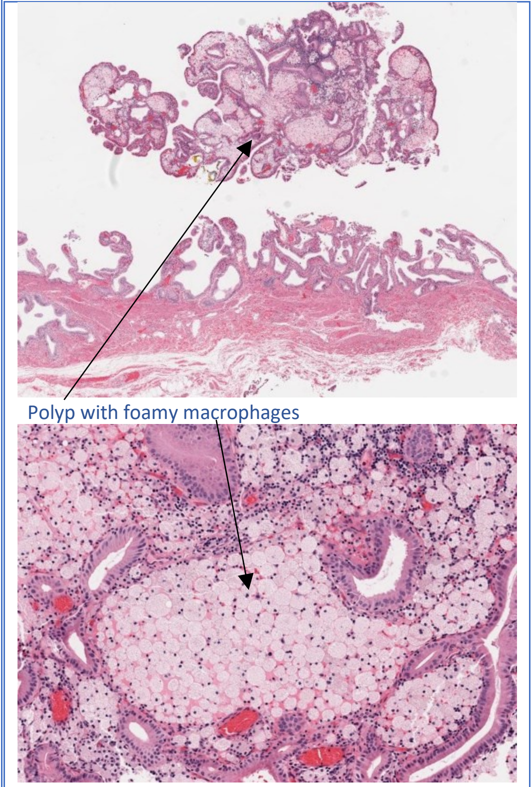
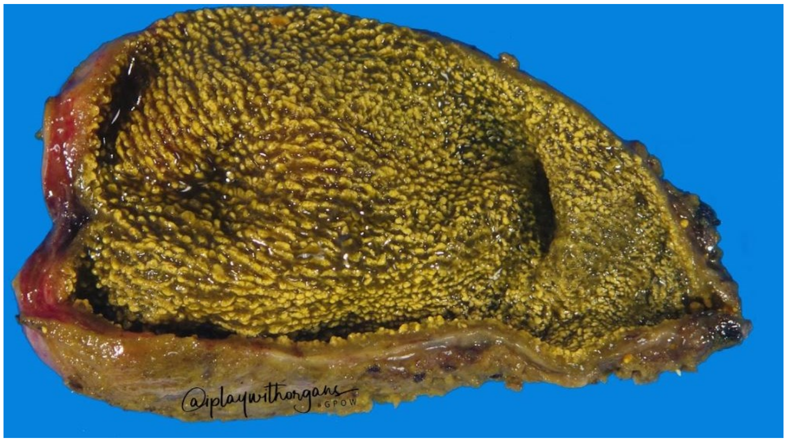


Polyp with foamy macrophages

CHOLESTEROL POLYP/CHOLESTEROLOSIS

MORPHOLOGY

- Gross: **Yellow flecks against a dark green background (strawberry gallbladder)** in cholesterolosis, and polypoid excrescences projecting into the lumen in cholesterol polyp
- Microscopy: Accumulation of **foamy macrophages** within lamina propria resulting in thickened folds or polyps and adjacent chronic inflammation if coexistent calculi present



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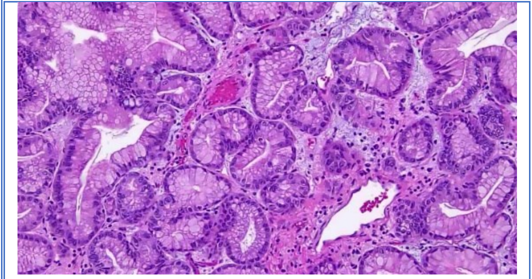
Gross photograph: Strawberry gallbladder (©Cory Nash, MD)



Tightly packed and dilated pyloric-type glands

PYLORIC GLAND ADENOMA (PGA)

MORPHOLOGY

- Gross: Sessile or pedunculated
- Microscopy: Non-invasive, benign glandular neoplasm composed of **mucinous glands with pyloric or Brunner gland-like features**
- Glands are tightly packed and maybe cystically dilated; cells feature abundant apical mucinous cytoplasm, peripheral nuclei, and minimal intervening stroma
- Paneth cells and neuroendocrine cells are often seen
- IHC: **CK7, MUC6**

7. PANCREATOBILIARY PATHOLOGY

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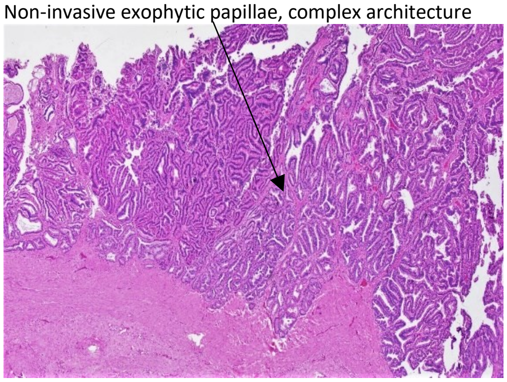
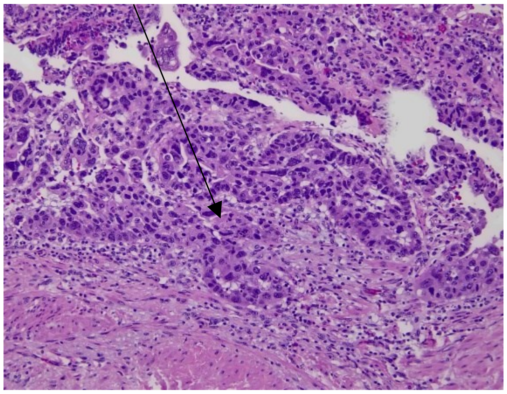
OTHER HIGH YIELD POINTS

- **CTNNB1 mutations and nuclear β-catenin** immunohistochemical expression in 60% of PGAs
- If an invasive component is not present, it is usually cured by cholecystectomy, even when high-grade dysplasia is present.

Non-invasive exophytic papillae, complex architecture



ICPN with invasive carcinoma



INTRACHOLECYSTIC PAPILLARY NEOPLASM (ICPN)

MORPHOLOGY

- Gross: **Granular, friable** excrescences or prominent **exophytic** growth, broad-based or with thin stalk which often detach into the lumen and mistaken as biliary sludge
- Microscopy: **Non-invasive back-to-back** epithelial units predominantly in **papillary or tubulopapillary** in the architecture
- Four morphological patterns, often with an intermixed pattern
- **Biliary-type:** most common, cuboidal cells with clear to eosinophilic cytoplasm, enlarged nuclei, and distinct nucleoli
- **Gastric-type:** elongated glands lined with tall columnar mucinous cells (resemble gastric foveolar epithelium) with abundant pale cytoplasm and peripheral nuclei
- **Intestinal-type:** resembles colonic adenomas, tall columnar cells with basophilic cytoplasm and pseudostratified cigar-shaped nuclei
- **Oncocytic-type:** least common, arborizing papillae lined by cells with abundant granular eosinophilic cytoplasm and nuclei with prominent nucleoli
- IHC: **Biliary type**: CK7+, MUC1+; **Gastric-type**: diffuse MUC5AC+ and some express MUC6; **Intestinal-type**: CK20+, CDX2+, MUC2+; **oncocytic-type**: MUC1+

OTHER HIGH YIELD POINTS

- ***KRAS*** mutation is common; TP53 and GNAS mutations are rare
- Invasive carcinoma is identified in half of the cases, particularly those with biliary morphology or high-grade dysplasia

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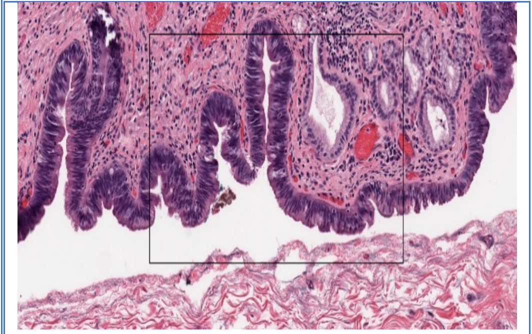
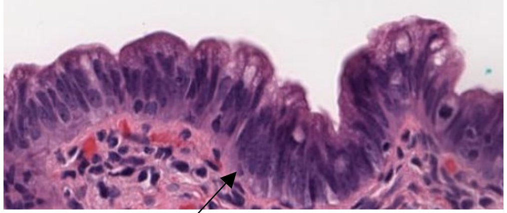


Low-grade BilIN



Nuclear stratification and preserved nuclear polarity

BILIARY INTRAEPITHELIAL NEOPLASIA (BilIN)

Features	Low-grade BilIN	High-grade BilIN
Microscopy	Flat or micropapillary Hyperchromatic nuclei High N: C ratio Nuclear stratification Preserved nuclear polarity	Flat or micropapillary Hyperchromatic, irregular nuclei High N: C ratio, pleomorphic, bizarre nuclei Complex nuclear stratification Loss of nuclear polarity
Biliary mucosal involvement	Relatively small foci	Relatively extensive
Peribiliary glands involvement	Infrequent	Frequent
IHC **Ki-67 labeling index**	Mildly to moderately increased	Markedly increased
S100	Mild to moderate	Diffuse and strong
p53	Wild-type	Frequently aberrant
p16	Relatively preserved	Decreased

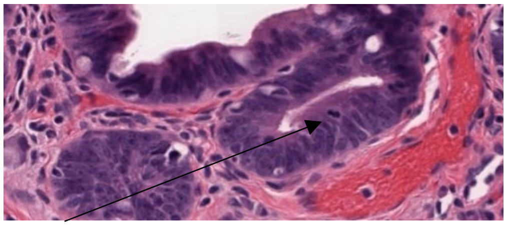
MORPHOLOGY

- Non-invasive flat or micropapillary dysplastic epithelial lesion confined to gallbladder lumen or biliary tree, grossly not visible. **Graded based on worst**

- **cytoarchitectural atypia** and is classified by current two-tiered grading system as low (includes previous BilIN-1 and 2) or high (previous BilIN-3)
- High-grade BilIN can extend to peribiliary glands and Rokitansky-Aschoff sinuses (feature should not be confused for invasion)

OTHER HIGH YIELD POINTS

- Cholelithiasis, FAP, Primary sclerosing cholangitis (PSC), choledochal cyst, and anomalous union of pancreatobiliary ducts are the **predisposing factors**
- **KRAS** mutations are seen in ~40% of cases (early molecular event), and TP53 mutations are late events in high-grade BilIN
- Low-grade BilIN is of no clinical significance
- Most cases of high-grade BilIN can be **cured by cholecystectomy**, usually multifocal disease due to a field effect and lead to recurrences and metastasis


Mitosis

Path Presenter

CARCINOMA OF GALLBLADDER

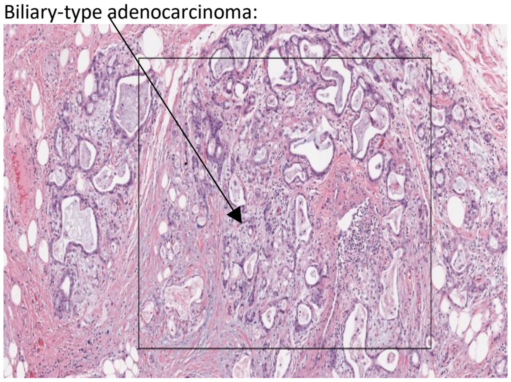
MORPHOLOGY

- Gross: Most carcinomas are located in the **fundus**, variable gross appearance- usually flat, firm, granular, and poorly defined
- Microscopy: Various histologic subtypes
- **Biliary-type adenocarcinoma**: Most common subtype, morphology, and behavior similar to pancreatic ductal adenocarcinoma, composed of infiltrating tubules lined with cuboidal cells embedded in a desmoplastic stroma.
- **Intestinal-type adenocarcinoma**: Resemble colonic adenocarcinoma, tubular configuration with columnar cells featuring elongated, pseudostratified nuclei, uncommon type so important to rule out a metastatic colonic adenocarcinoma
- **Mucinous adenocarcinoma**: >50% of the tumor contains extracellular mucin with single cells or strips of neoplastic cells floating in mucin and is more aggressive than ordinary gallbladder carcinomas
- **Clear cell carcinoma**: Sheets of clear cells in an alveolar arrangement separated by sinusoidal vessels mimic clear cell renal cell carcinoma
- **Poorly-cohesive carcinoma ± signet-ring cells**: Poorly cohesive individual cells or cords forming a diffuse infiltrative pattern and is more aggressive than ordinary gallbladder carcinomas
- **Adenosquamous carcinoma**: Squamous elements constitute ≥25% of the tumor admixed with an adenocarcinoma component
- **Squamous cell carcinoma**: Rare type with an aggressive behavior

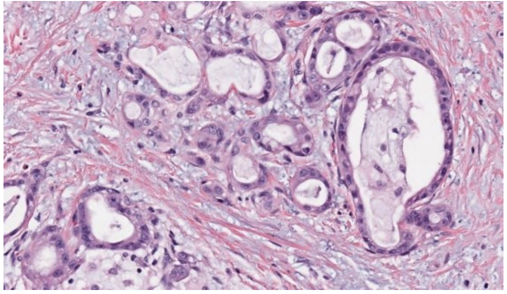
OTHER HIGH YIELD POINTS

- Most common biliary tract carcinoma, more frequent in females
- **Risk factors**: Gall stones (most common), PSC, aflatoxin B1, infections (Salmonella typhi, Opisthorchis viverrini), pancreatobiliary maljunction, syndromic predisposition (FAP, Lynch)
- **TP53** mutations are seen in >50% of cases; other common mutations include **CDKN2A or CDKN2B, ARID1A, PIK3CA, and CTNNB1**
- The **tumor stage is the most important prognostic factor**, early gallbladder carcinomas (Tis/T1a/T1b) have a better prognosis compared to the advanced ones, and in T2 tumors: T2a (tumor invades peritoneal side connective tissue) has a better prognosis than T2b (tumor invades hepatic side)

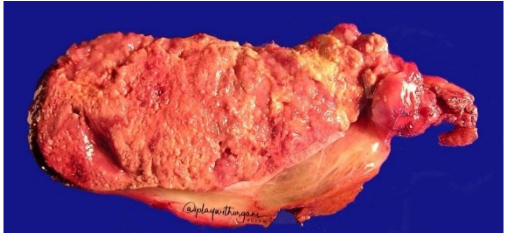
Biliary-type adenocarcinoma:



Cuboidal cells lined infiltrating tubules



Gross: Flat, firm, granular, and poorly defined



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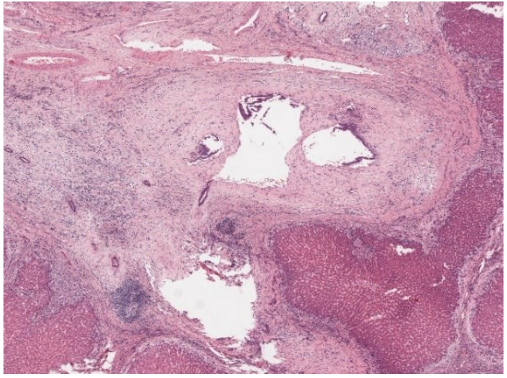
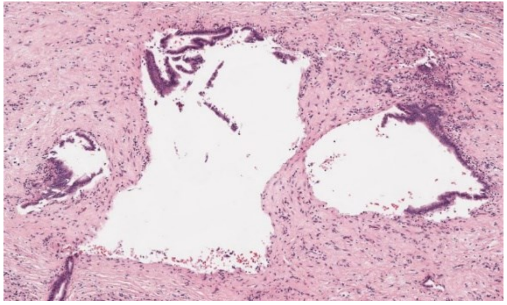
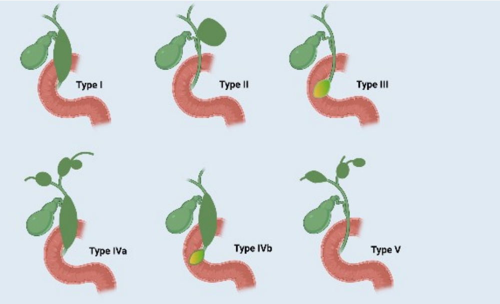
Cystic dilatation of the biliary tree



Cystic dilatation of the biliary tree



Todani classification: created using Biorender by Manju Ambelil, MD



Path Presenter

CHOLEDOCHAL CYSTS

MORPHOLOGY

- **Cystic dilatation of the biliary tree**; predominant in the **pediatric** population, and most patients have an anomalous pancreatobiliary junction which may result in reflux of pancreatic enzymes to the bile duct
- Gross: Fibrotic cyst wall with variable sizes, contains bile or stones and shows a distal narrowing
- Microscopy: **Cyst wall** composed of **dense fibrous** tissue featuring variable amount of **smooth muscle and chronic inflammation**, a columnar epithelial lining may be focally seen and most often is damaged and denuded

OTHER HIGH YIELD POINTS

- **Increased risk** of developing carcinoma, risk increases with age
- Other complications include pancreatitis, cholelithiasis, cholangitis, secondary biliary cirrhosis, and spontaneous rupture
- Todani classification of choledochal cyst

Type	Findings
I	Segmental or Fusiform dilatation of common bile duct
II	Focal saccular dilatation or diverticulum of common bile duct
III	Cystic dilatation of common bile duct within the duodenal wall (choledochocele)
IVa	Combined intrahepatic and extrahepatic cystic dilatation of bile ducts
IVb	Multiple cystic dilatations of extrahepatic bile duct only
V	Multiple intrahepatic biliary cysts (Caroli disease)

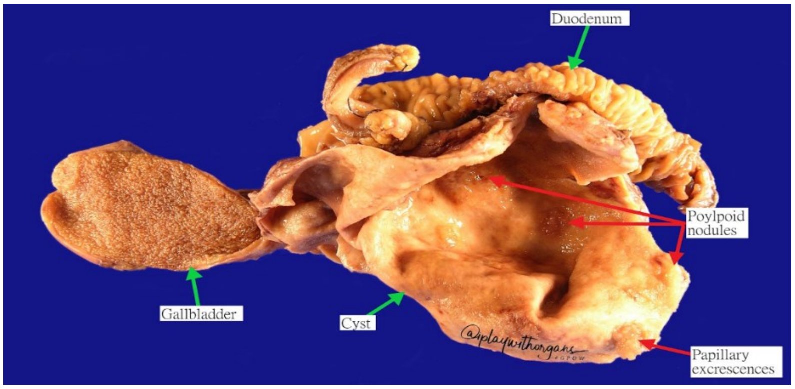
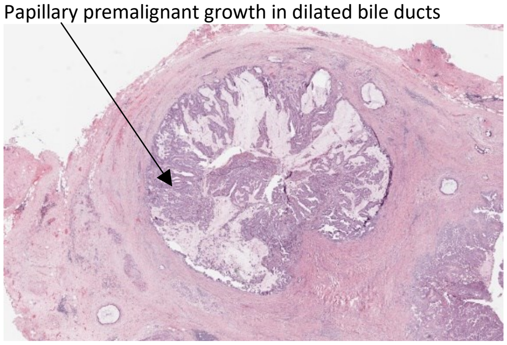


Image credits: Cory Nash

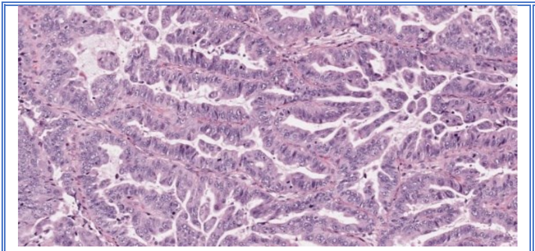
Papillary premalignant growth in dilated bile ducts



INTRADUCTAL PAPILLARY NEOPLASM OF THE BILE DUCTS (IPNB)

MORPHOLOGY

- Gross: **Polypoid or papillary** premalignant growth in dilated bile ducts which can lead to obstruction and duct dilatation
- Microscopy: Papillary structures with fine fibrovascular cores covered by cuboidal or columnar epithelial cells, which show intestinal, biliary, gastric-type, or oncocytic differentiation like in ICPN, with variable cytologic atypia
- Two-tiered grading system, low and high-grade dysplasia
- Recently proposed classification divide IPNB into type 1 and type 2
    - **Type 1:** histologically similar to **IPMN** of the pancreas, with a regular papillary/villous growth pattern, mucin production, more frequent in **intrahepatic** bile ducts, and **less aggressive**



Intraductal papillary growth

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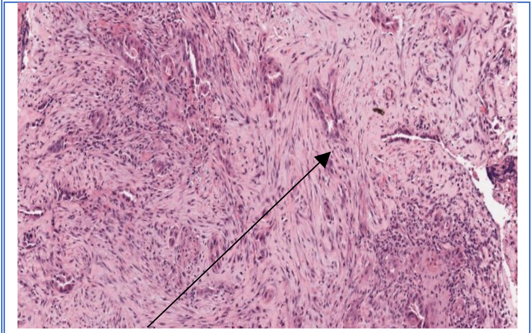
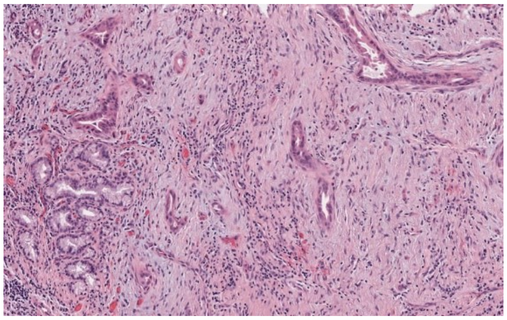
  - **Type 2:** irregular papillae with **cribriform and solid** areas, rare mucin production, frequent in **extrahepatic** bile ducts, and **more aggressive**

OTHER HIGH YIELD POINTS

- Risk factors include PSC, hepatolithiasis, and liver fluke infection (clonorchiasis and opisthorchiasis)
- **KRAS, GNAS, and RNF4** mutations in those with **mucinous** morphology/**low-grade** dysplasia and **TP53 mutations in high-grade neoplasms**
- Prognosis depends on the presence of invasive carcinoma, but still, IPNB with invasive carcinoma have a **better prognosis than conventional cholangiocarcinoma**



Irregular glands and tumor clusters in desmoplastic stroma



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CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS

MORPHOLOGY

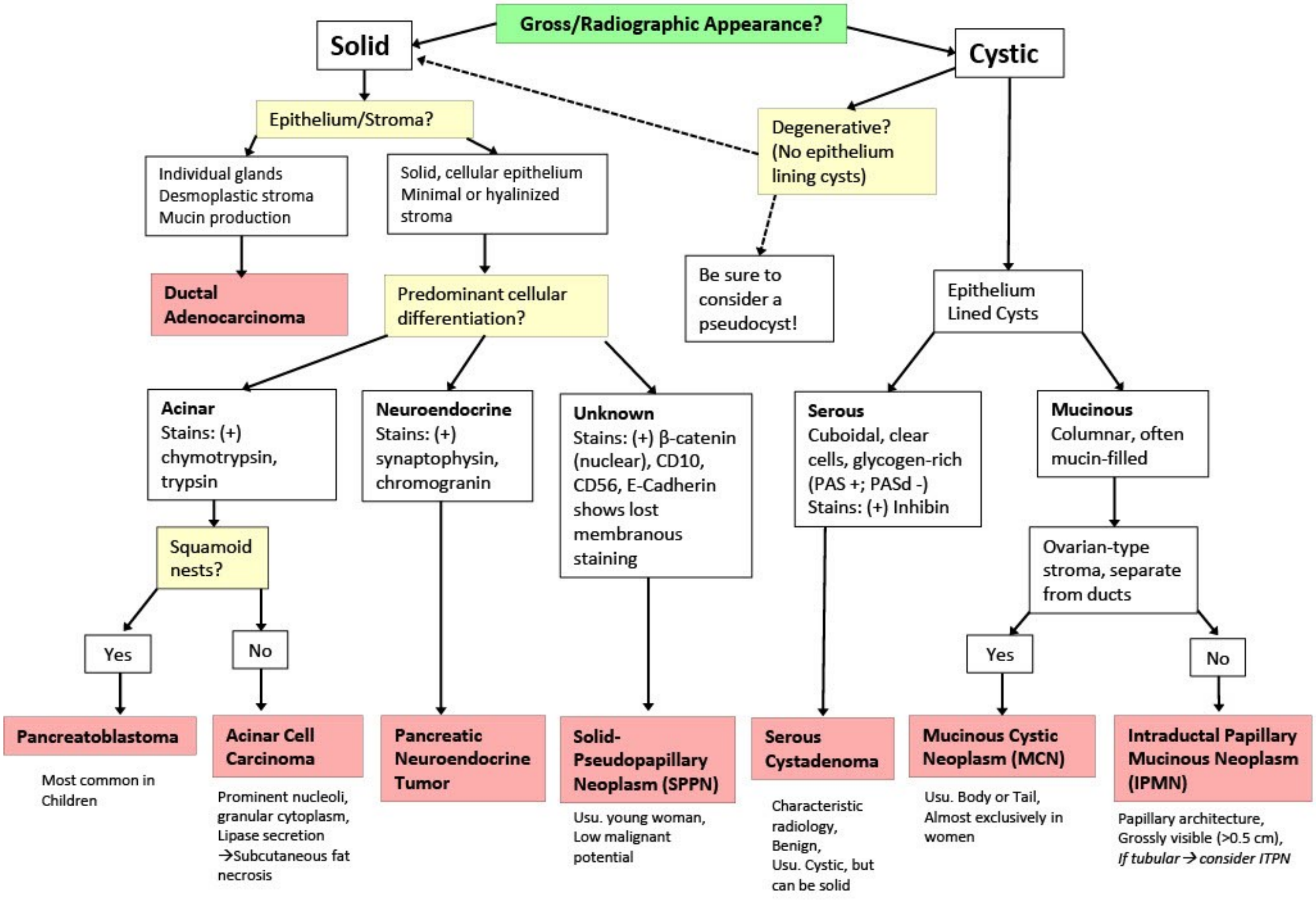
- Gross: **Sclerosing** (most common), nodular or papillary growths
- Microscopy: Most carcinomas are **pancreatobiliary-type** adenocarcinoma/cholangiocarcinoma, with widely spaced, irregular glands and small tumor clusters infiltrating through desmoplastic stroma and frequently with perineural and lymphovascular invasion
- Other histologic patterns of adenocarcinoma include intestinal-type, foveolar-type, mucinous, signet-ring cell, clear cell, hepatoid, and micropapillary-type
- Rare subtypes: squamous cell, adenosquamous, sarcomatoid, and undifferentiated carcinomas
- IHC: **CK7, CK19, CEA, CA19-9**

OTHER HIGH YIELD POINTS

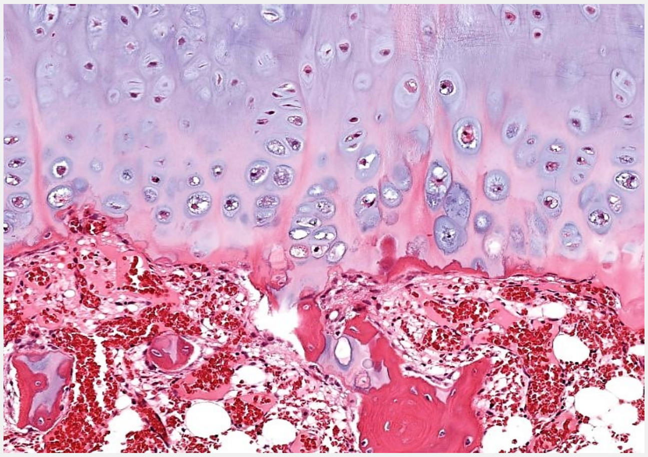
- Risk factors: PSC, cholelithiasis, choledochal cysts, and liver fluke infection (Clonorchis Sinensis and Opisthorchis viverrini)
- BilIN and IPNB are precursor lesions
- **Klatskin tumors: Perihilar** tumors occurring at the confluence of the right and left hepatic ducts
- **KRAS** mutations are early events, followed by **TP53** mutations (these can be seen in intrahepatic cholangiocarcinoma also)
- Extrahepatic cholangiocarcinomas specific alterations are PRKACA/PRKACB fusions, ELF3 and ARID1B mutations
- **Poor prognosis** depends on the stage at presentation and resectability

Diagnostic Algorithm for Pancreatic Tumors

Figure adapted from WHO


Gross/Radiographic Appearance?
Solid
Cystic
Epithelium/Stroma?
Individual glands
Desmoplastic stroma
Mucin production
Solid, cellular epithelium
Minimal or hyalinized stroma
Ductal Adenocarcinoma
Predominant cellular differentiation?
Degenerative? (No epithelium lining cysts)
Be sure to consider a pseudocyst!
Epithelium Lined Cysts
Acinar
Stains: (+) chymotrypsin, trypsin
Neuroendocrine
Stains: (+) synaptophysin, chromogranin
Unknown
Stains: (+) β-catenin (nuclear), CD10, CD56, E-Cadherin shows lost membranous staining
Serous
Cuboidal, clear cells, glycogen-rich (PAS +; PASd -)
Stains: (+) Inhibin
Mucinous
Columnar, often mucin-filled
Squamoid nests?
Yes
No
Ovarian-type stroma, separate from ducts
Yes
No
Pancreatoblastoma
Most common in Children
Acinar Cell Carcinoma
Prominent nucleoli, granular cytoplasm, Lipase secretion →Subcutaneous fat necrosis
Pancreatic Neuroendocrine Tumor
Solid-Pseudopapillary Neoplasm (SPPN)
Usu. young woman, Low malignant potential
Serous Cystadenoma
Characteristic radiology, Benign, Usu. Cystic, but can be solid
Mucinous Cystic Neoplasm (MCN)
Usu. Body or Tail, Almost exclusively in women
Intraductal Papillary Mucinous Neoplasm (IPMN)
Papillary architecture, Grossly visible (>0.5 cm), *If tubular → consider ITPN*

Ductal Adenocarcinoma	Chronic Pancreatitis
Haphazard, irregular architecture	Lobular, organized architecture
Incomplete luminal spaces with gland rupture	Complete luminal spaces
Cellular pleomorphism (4:1 variation in size)	Less pleomorphic
Perineural invasion	Absent
Vascular/perivascular invasion	Absent
Extrapancreatic invasion	Absent
Mitoses and nucleoli are often prominent	Often absent
Can extend outside of the pancreas into fat, etc.	Confined to pancreas



Osteochondroma (H&E stain). Courtesy: Akanksha Gupta, MD

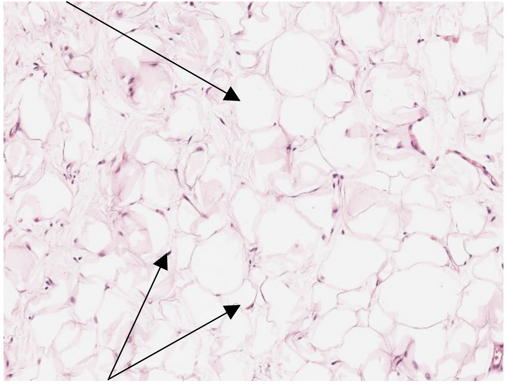
CHAPTER 8: BONE AND SOFT TISSUE PATHOLOGY

Terrance Lynn, MD
Kenechukwu Ojukwu, MD
Manita Chaum, MD
Amandeep Kaur, MD
Snehal Sonawane, MD
Dinesh Pradhan, MD

Image courtesy: Cedars Sinai Medical Center, Department of Pathology and Lab Medicine, Los Angeles, CA (images contributed by Dr Bonnie Balzer, Vice Chair of Department)

8. BONE AND SOFT TISSUE PATHOLOGY

ADIPOCYTIC TUMORS



LIPOMA

MORPHOLOGY

- **Mature adipocytes** with single large fat droplet and eccentric nuclei

OTHER HIGH YIELD POINTS

- Clinically presents as a **painless** mass and is superficial/subcutaneous
- Most common mesenchymal tumor in adults, M=F
- **Gross exam**: **well-circumscribed**, **homogenous cut surface**, <5 cm
- If retroperitoneal/large, **must** exclude well-differentiated liposarcoma
- **Recurrence uncommon**, slightly higher risk if incompletely resected
- **FISH:** Absence of MDM2 amplification
- **Molecular:** Rearrangements of *HMGA1, HMGA2*

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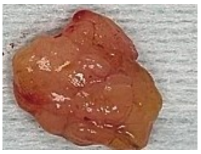
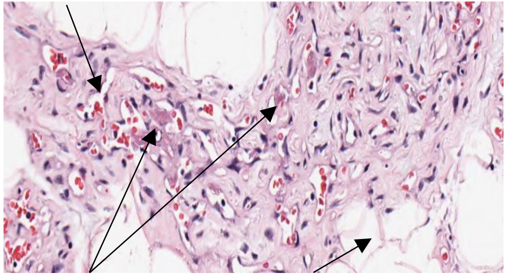


Courtesy of
John Cummings



ANGIOLIPOMA

MORPHOLOGY

- Mature adipocytes, **branching vascular network, fibrin thrombi**

OTHER HIGH YIELD POINTS

- Clinically presents as a **painful** mass on the forearm
- Seen in 2-3rd decade with male predominance
- Gross: Circumscribed dense nodule, <2cm, and vascular
- **Molecular:** *PRKD2* mutations (>80%), activating *PIK3CA* seen also

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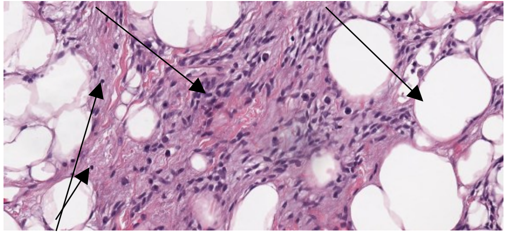

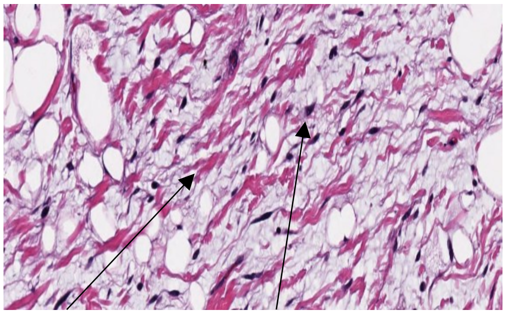

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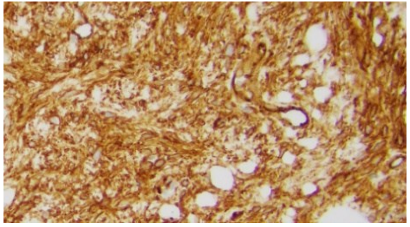
SPINDLE CELL & PLEOMORPHIC LIPOMA

MORPHOLOGY

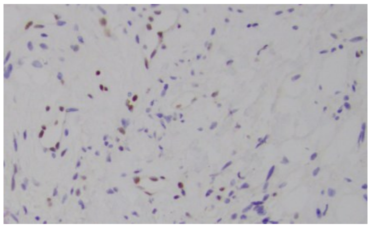
- **Mature adipocytes** with bland **spindle cells** and **ropey collagen**
- Variable myxoid background and mast cells

OTHER HIGH YIELD POINTS

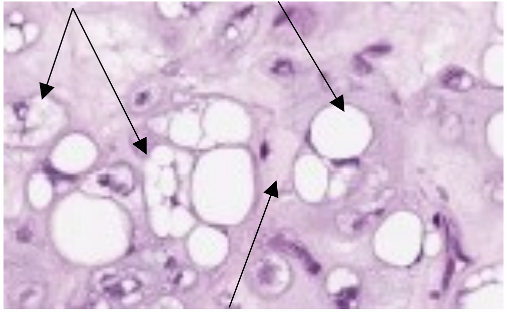
- **Uncommon** tumor with **cape-like distribution**: Neck, shoulder, back
- Mainly **middle age** to **elderly men**
- **Can have a spectrum of histology**: can be primarily fatty with minimal spindle cells, or can have minimal fat and composed of largely spindle cell component → mimics DFSP
- **Pleomorphic lipoma**: ropey collagen, pleomorphic spindle & **floret** cells, myxoid background
- **Floret cells**: giant cells with multiple nuclei arranged along the peripheral edge and central eosinophilic cytoplasm
- **IHC:** Spindle & floret cells → CD34+, loss of nuclear Rb1



CD34+



Loss of nuclear Rb1


Lipoblast-like cells
Adipocytes
Myxochondroid background

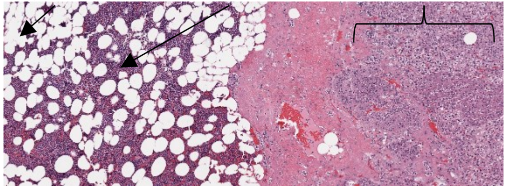
CHONDROID LIPOMA

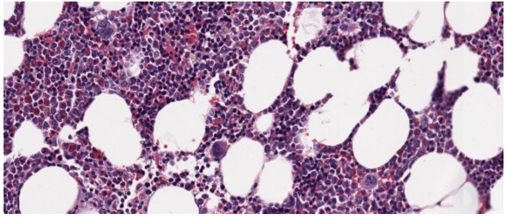
MORPHOLOGY

- Nests/cords of "**lipoblast-like**" or **chondrocyte-like** vacuolated cells
- **Chondromyxoid background**
- Prominent **vascular network** +/- hemorrhage
- **Absence of pleomorphism**, **atypia**, mitoses, necrosis

OTHER HIGH YIELD POINTS

- Predominantly in **females**, 3rd-4th decade
- Mostly seen in **limb girdles/proximal** extremities
- No metastasis, no recurrence
- **Molecular: t(11;16)(q13;p12-13) translocation** → fusion of **C11orf95** and **MRTFB** genes


Adipose & hematopoietic elements
Adrenal


Normal hematopoietic elements

MYELOLIPOMA

MORPHOLOGY

- **Mature adipocytes** with **normal marrow elements**
- Often have adjacent adrenal parenchyma

OTHER HIGH YIELD POINTS

- Most common in the **adrenal medulla**
- Presents in 5-7th decade, **M=F**, **unilateral**, imaging is diagnostic
- Can become very large and weigh in kgs
- **Grossly**: Adipose tissue with hemorrhage (from marrow)
- No association with hematopoietic disorders
- **Pathogenesis:** unknown
- **Primary differential:** extramedullary hematopoiesis

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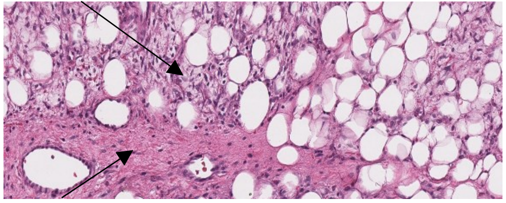
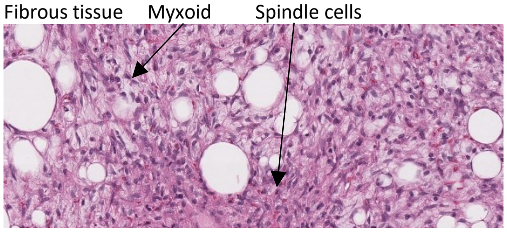

Immature adipocytes
Fibrous tissue


Myxoid
Spindle cells

LIPOBLASTOMA

MORPHOLOGY

- **Immature adipocytes** separated by connective tissue that has a loose myxoid appearance
- Adipocytes are seen at various points of maturation (including **spindle cells**)
- **Plexiform vascular** pattern

OTHER HIGH YIELD POINTS

- Rare tumors seen in infants, **male predominance**
- Presents as a **painless** soft tissue mass
- Localized → Lipoblastoma; Diffuse→ Lipoblastomatosis
- Molecular: Chromosomal rearrangement of 8q11 →**HAS2-PLAG1** and **COL1A2-PLAG1; t(3;8)(p13;q21.1)** also seen

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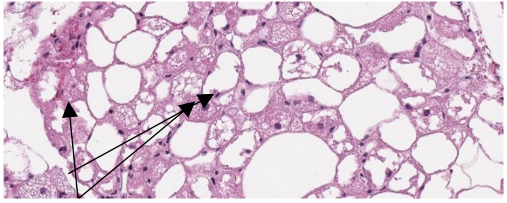

Organoid
Brown adipocytes

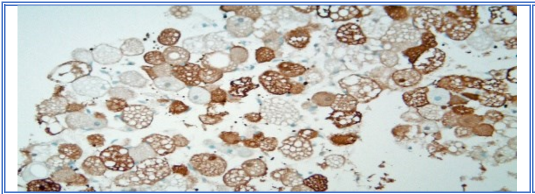
HIBERNOMA

MORPHOLOGY

- **Organoid arrangement** of **brown adipocytes** with **granular** and **vacuolated cytoplasm**
- Vacuoles in adipocytes are **small** and **uniform**
- Delicate **branching capillaries**

OTHER HIGH YIELD POINTS

- Rare tumor, seen in 3rd – 4th decade, no sex predilection
- Common locations: thigh, axilla, back



- Can **produce steroids**
- IHC**:** generally not needed, but **UCP-1+, S100+, CD34-** (+ in spindle variant)
- **Molecular**: may have rearrangements in 11q13-21

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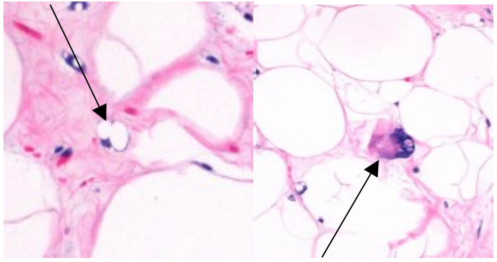
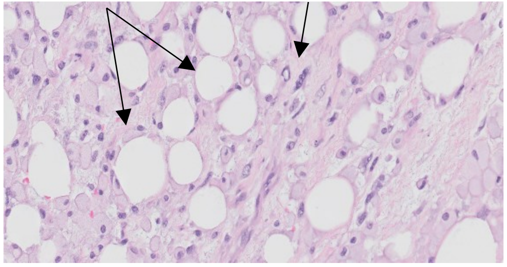
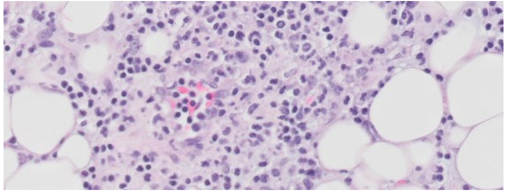






Path Presenter

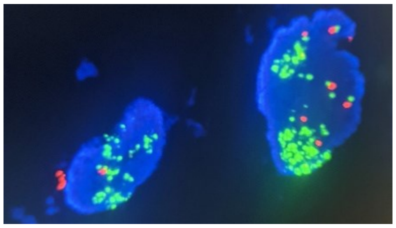
ATYPICAL LIPOMATOUS TUMOR (WELL-DIFFERENTIATED LIPOSARCOMA)

MORPHOLOGY

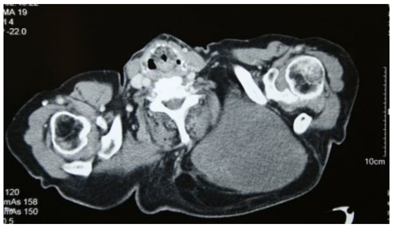
- Variable amounts of **lipoblasts and mature adipocytes**
- **Atypical** cells **most commonly seen** near/in the **fibrous septae**

OTHER HIGH YIELD POINTS

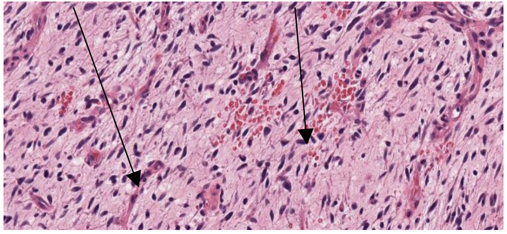
- **Most common form** of liposarcoma
- Often are large, >10 cm
- No metastatic potential but recurs locally and can de-differentiate
- Subtypes:
  - **Lipoma-like:** Most common, frequently contain lipoblasts, grossly indistinguishable from lipoma
  - **Sclerosing type:** Second most common, usually paratesticular, or retroperitoneal, has collagenous fibrosis with scattered atypical multinucleated stromal cells
  - **Inflammatory:** Rare, chronic inflammatory cells (more commonly B>T) in a fibrocollagenous stroma, rare, atypical multinucleated cells
  - **Mixed:** Combination of the above
- **IHC**: **S100+, MDM2+,** CDK4+, p16+; less common: CD34+, Desmin+
- **FISH:** for **MDM2 and CDK4 amplification (can use real-time PCR)**

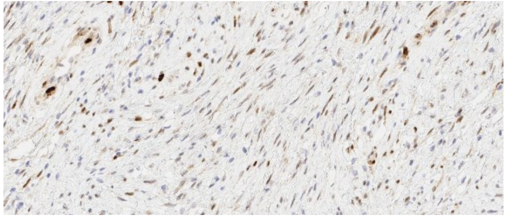


MDM2 amplification using FISH courtesy of: Amal Alodaini @DrAlodaini



Radiology of Liposarcoma courtesy of Dr. Panoraia Paraskeva





Credit: Raul Perret, MD, MSc @kells108

DEDIFFERENTIATED LIPOSARCOMA

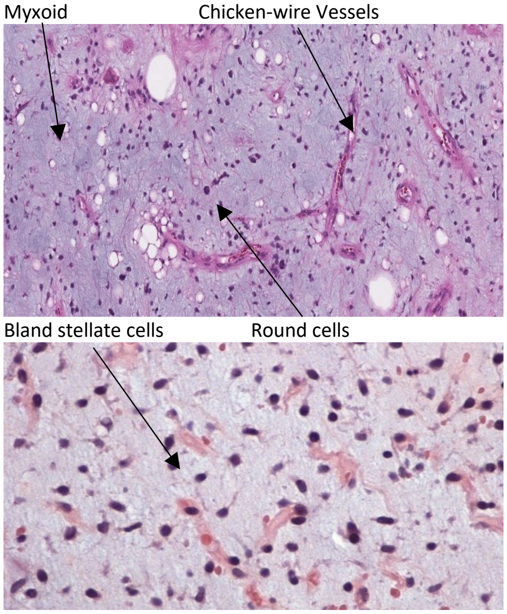
MORPHOLOGY

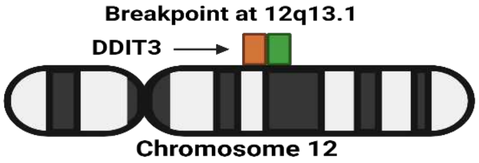
- High grade component has entrapped lipoblasts and often looks sarcomatous (like fibrosarcoma) and has **multinucleated cells, pleomorphic cells, and/or spindled cells**
- Low grade component may resemble fibromatosis
- **Delicate branching vessels**

OTHER HIGH YIELD POINTS

- Better prognosis than other high-grade sarcomas
- Most common site is retroperitoneum, also in extremities and spermatic cord
- Metastasizes in 15-20% of cases, recurs in ~40-50%
- IHC: MDM2+, CDK4+
- Molecular:
  - Amplification of **12q14**
  - FISH for **MDM2** and **CDK4** amplification (can use real-time PCR)

Path Presenter


Myxoid
Chicken-wire Vessels
Bland stellate cells
Round cells


Breakpoint at 12q13.1
DDIT3
Chromosome 12

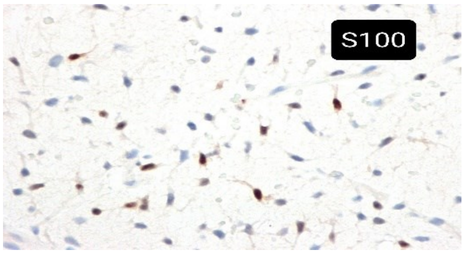
MYXOID LIPOSARCOMA

MORPHOLOGY

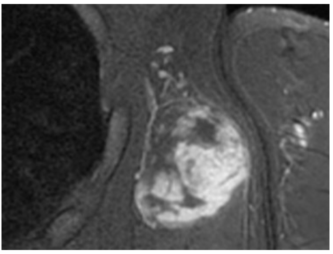
- Proliferation of bland monomorphic **stellate and fusiform cells**
- High-grade → cells are **rounded** and **more primitive**
- Abundant **myxoid matrix** and **chicken-wire vasculature**
- Lipoblasts with variable vacuolation

OTHER HIGH YIELD POINTS

- Usually in younger individuals, most common in thigh
- Higher grade → less myxoid component and more-round cell
- Metastasizes in 10-60% of cases (risk varies by grade), recurs in ~30%
- IHC: Positive for **DDIT3 and S100**; negative for MDM2 and CDK4
- **Molecular/FISH**: ***FUS-DDIT3*** → **t(12;16)(q13;p11.2)**
    - **Uncommon**: EWSR1-DDIT3 → t(12;22)(q13;q12)

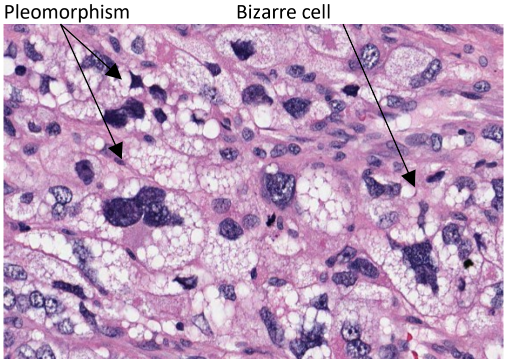


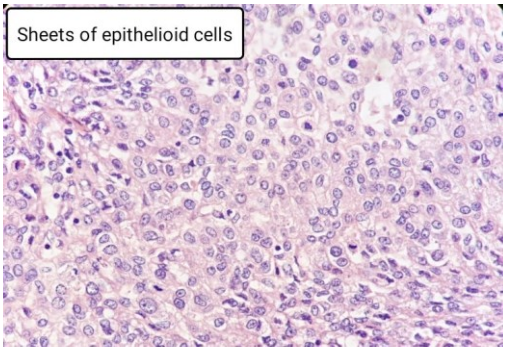
Credit: Raul Perret, MD, MSc @kells108



Courtesy of Dr. Jordi M I Nogue

Path Presenter


Pleomorphism
Bizarre cell


Sheets of epithelioid cells

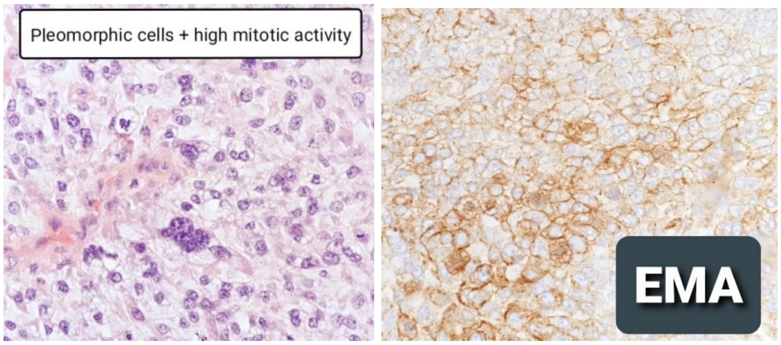
PLEOMORPHIC LIPOSARCOMA

MORPHOLOGY

- **Pleomorphic cells (giant, bizarre**), lipoblasts, many mitoses, necrosis

OTHER HIGH YIELD POINTS

- Least common liposarcoma
- **Grossly**: large, multi-nodular, and white-yellow, foci of necrosis
- **Molecular**: negative MDM2 and CDK4
    - Complex karyotype but not specific

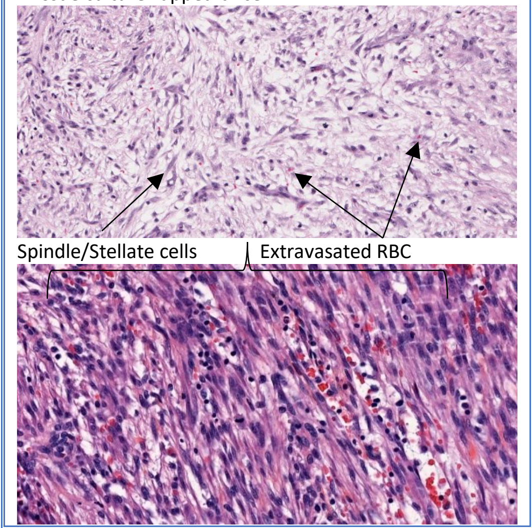

Pleomorphic cells + high mitotic activity
EMA

Pleomorphic liposarcoma : Epithelioid variant: Predominance of epithelioid cells (may express EMA/CK) Credit: Raul Perret, MD, MSc @kells108

Path Presenter

FIBROBLASTIC & MYOFIBROBLASTIC TUMORS

“Tissue culture” appearance



NODULAR FASCIITIS

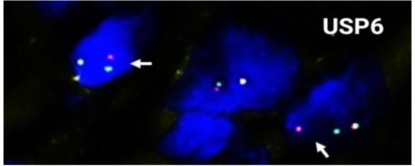
MORPHOLOGY

- **Bland stellate/spindle cells** with a “**tissue culture**” pattern
- **Torn stroma** with “S” and “C” shapes
- **Extravasated red blood cells**
- Older lesions are collagenous/scarred

OTHER HIGH YIELD POINTS

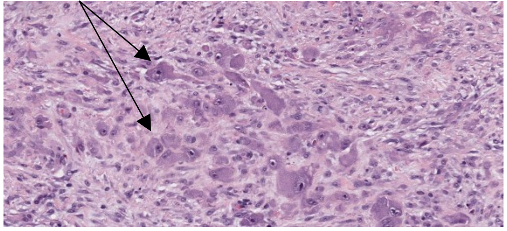
- **Benign, self-limiting**, rapid growth, **mass-forming** subcutaneous lesion
- Most common in the **upper extremity** or **head** and **neck** of **kids**
- **Variants**: Ossifying fasciitis, intravascular fasciitis, cranial fasciitis
- **IHC**: **SMA+, MSA+, Calponin+, Desmin-**
- Molecular: **MYH9-USP6;** Other partners: ***COL1A1*, *CTNNB1*, others**
- FISH: USP6 break-apart probe

Path Presenter

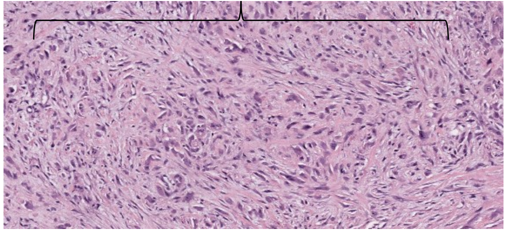


Credit: Raul Perret, MD, MSc @kells108

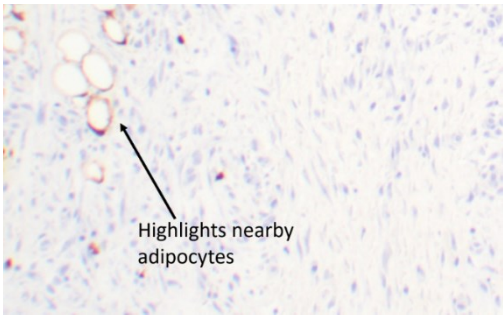
Ganglion-like cells



“Tissue culture” appearance



S100 IHC



Path Presenter

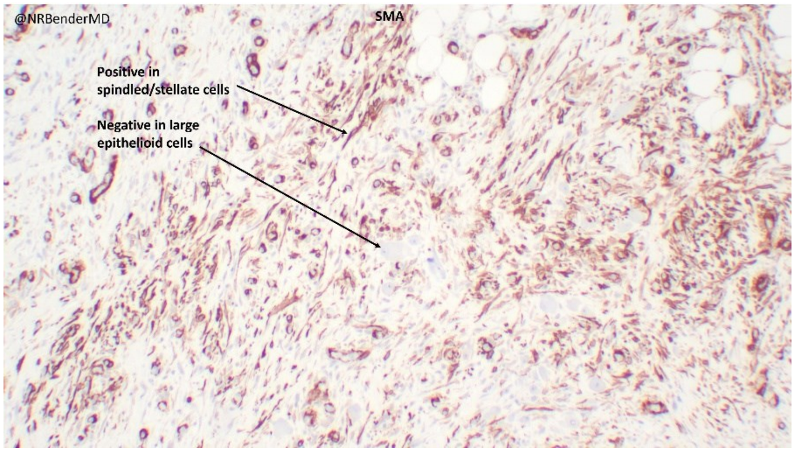
PROLIFERATIVE FASCIITIS/MYOSITIS

MORPHOLOGY

- “**Tissue culture**” pattern of prominent large, basophilic **ganglion-like cells** with one or more vesicular nuclei with conspicuous nucleoli
- **Extravasated red blood cells** and **arborizing vascular network**
- Variable mitotic activity but no atypical mitosis

OTHER HIGH YIELD POINTS

- **Most commonly seen** in **adults** (>50) on the **forearm**
- **Rapidly growing**, **poorly circumscribed** mass but **benign**
- If arising in muscle → Proliferative myositis
- **Childhood variant** → **more cellular**, **pleomorphic ganglion-like** cells with a “rhabdomyoblastic” look; can have necrosis and many mitoses and inflammation; pushing border (unlike adults → infiltrative)
- **IHC**: SMA+, MSA+; Ganglion-like cells → vimentin


@NRBenderMD
SMA
Positive in spindled/stellate cells
Negative in large epithelioid cells

Credits: Nicole Bender @NRBenderMD

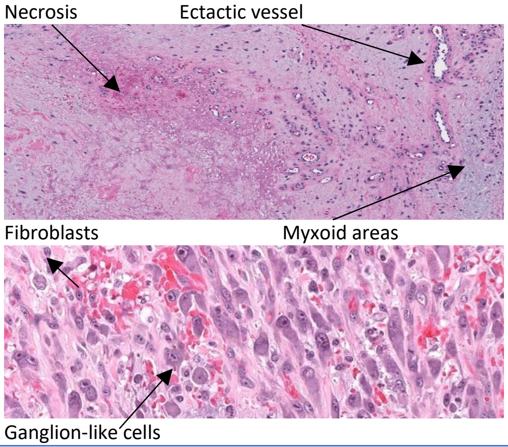
ISCHEMIC FASCIITIS

MORPHOLOGY

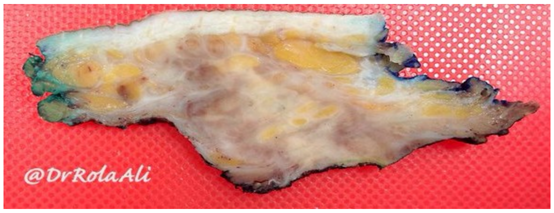
- **Zonal fibrinoid necrosis** with **prominent myxoid areas**
- Ectatic, **thin-walled blood vessels** +/- atypical endothelial cells
- Fibroblasts with degenerative changes → mimic **ganglion-like cells**

OTHER HIGH YIELD POINTS

- Occurs in immobilized individuals in shoulder, coccyx, chest wall


Necrosis
Ectactic vessel
Fibroblasts
Myxoid areas
Ganglion-like cells

Path Presenter



Credits: Rola Ali, MD @DrRolaAli

ELASTOFIBROMA

MORPHOLOGY

- **Thickened and fragmented elastic fibers**, **collagenous stroma** & variable fat

OTHER HIGH YIELD POINTS

- Association → **repetitive physical movements**
- Female predominance, **older age** (>50 years)
- Site → Scapula (inferior margin) on chest wall
- Clinically **slow growing painless** mass, Size → 3-10 cm
- **Gross**: Tan-**white to yellow firm mass** with poorly defined margins
- **Special stains: Elastin stain** → highlights abnormal elastic fibers
- Molecular: X-inactivation or gains of Xq; Rearrangements in 1p and 7q

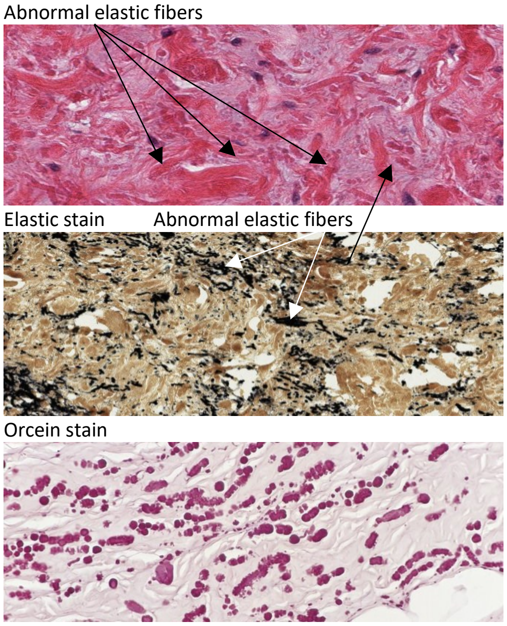

Abnormal elastic fibers
Elastic stain
Abnormal elastic fibers
Orcein stain

Image Credit: Raul Perret, MD, MSc @kells108

Path Presenter

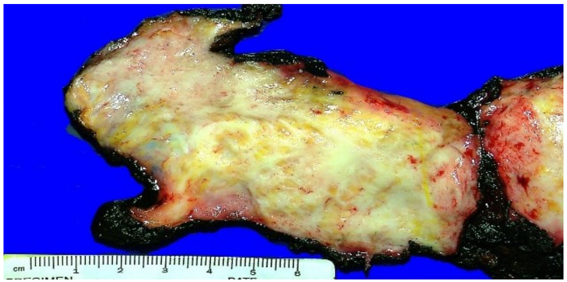


Image credit: Dr. Christina Arnold @CArnold GI

NUCHAL-TYPE FIBROMA

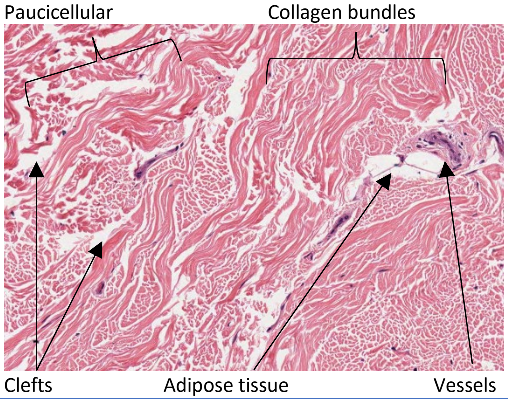
MORPHOLOGY

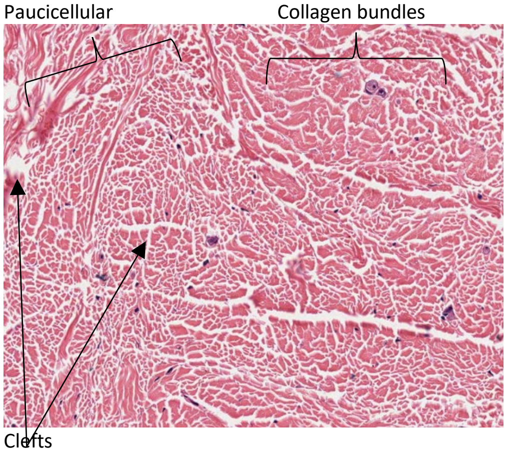
- Paucicellular **fibrocollagenous** proliferation composed of **patternless collagen** bundles separated by **clefts** (artifactual separation)
- Can have entrapped nerves, adnexal structures, vessels, or fat

OTHER HIGH YIELD POINTS

- Most commonly occurs on the posterior neck
- Strong male predominance, 3rd-5th decade of life
- Clinically: Solitary and painless mass
- IHC: CD34+ spindle cells; Negative nuclear beta-catenin, SMA, desmin

Path Presenter


Paucicellular
Collagen bundles
Clefts
Adipose tissue
Vessels



GARDNER-TYPE FIBROMA

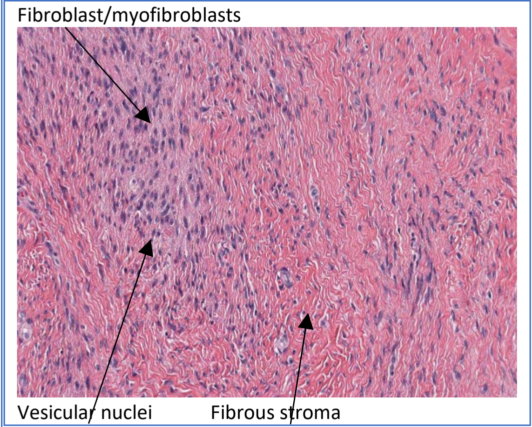
MORPHOLOGY

- Patternless proliferation of **paucicellular collagen bundles** separated by **clefts** (artifactual separation)
- Infiltrative growth pattern +/-trapped fat, vessels, and nerves

OTHER HIGH YIELD POINTS

- **Rare benign tumor**, may occur **sporadically** or be **syndromic**
- **FAP Syndrome** → adenomatous polyps, osteomas, Epidermoid & Dermoid cysts, Gardner fibroma
- Often seen in the **first decade** of life, **slight male predominance**
- Occurs mostly in the **subcutis of the back** and **paraspinal**
- **IHC**: Positive nuclear **Beta-catenin**
- **Molecular:** Germline ***APC*** gene mutation in FAP

Path Presenter



FIBROMA OF TENDON SHEATH

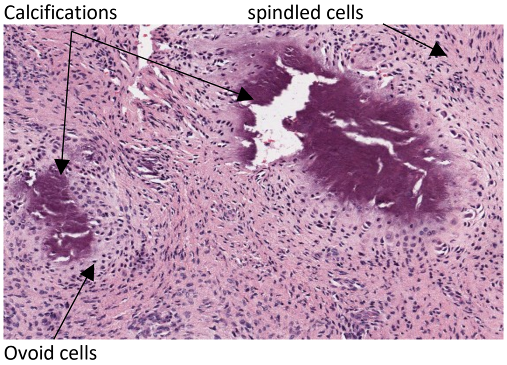
MORPHOLOGY

- Proliferation of **fibroblasts and myofibroblasts** with vesicular nuclei, single conspicuous nucleolus, and abundant granular eosinophilic to amphophilic cytoplasm
- "**Slit-like**" spaces seen at peripheral edge lined by flat endothelial cells
- Variable fibromyxoid stroma +/- cystic areas and storiform foci

OTHER HIGH YIELD POINTS

- Uncommon benign lesion, often middle-aged Males >> females
- Most common site is **upper extremities** (**~80% occur in hand**, mostly fingers)
- IHC: **Focal SMA +**; Desmin –
- **Molecular**: ***USP6* gene rearrangements** (similarly to nodular fasciitis)

Path Presenter



CALCIFYING APONEUROTIC FIBROMA

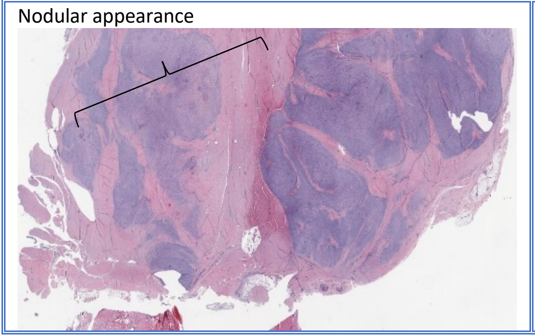
MORPHOLOGY

- Ovoid to spindled fibroblasts lacking nuclear atypia in a background of collagenous stroma with variable cellularity
- Scattered calcifications or cartilaginous foci with rimming by osteoclastic-like giant cells
- Absence of mitoses

OTHER HIGH YIELD POINTS

- Rare, occurring mostly in male children on finger or palm
- Local recurrence ~50%

Path Presenter



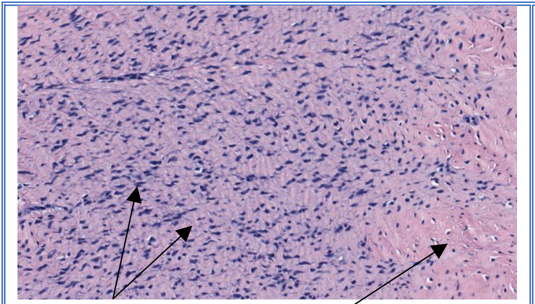
FIBROMATOSIS

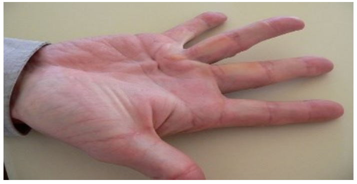
MORPHOLOGY

- Infiltrative **proliferation of myofibroblasts** in **sweeping fascicles**
- Myofibroblasts have **regularly spaced nuclei** with **smooth** nuclear **contours**, small **conspicuous nucleolus**, and **lack atypia**; **cytoplasm** can be **stellate**
- **Collagen in the background** (can be keloidal-like) with **small vessels** and occasional lymphocytic infiltrate and scattered giant cells

OTHER HIGH YIELD POINTS

- **Variable presentation** in males and females based on subtypes, recurrence common

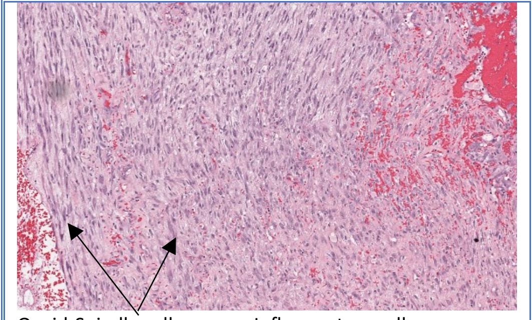


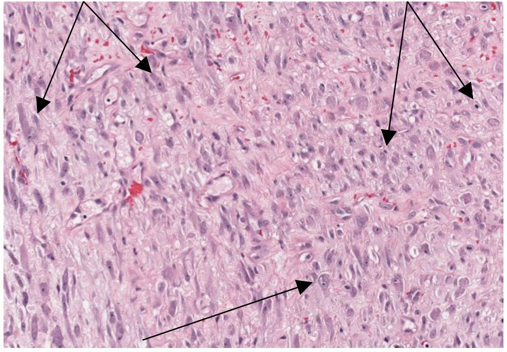


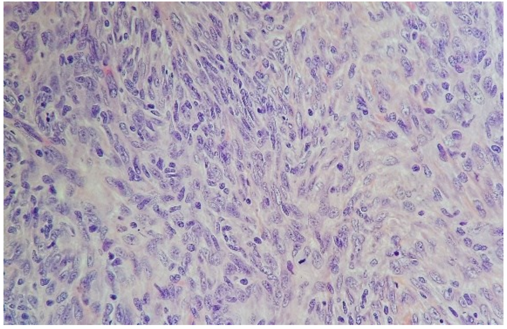
Path Presenter

Courtesy of Dr. Frank C. Muller

  - **Palmar (Dupuytren Contracture):** volar surface nodular myofibroblastic proliferation, predominantly male adults >50 years old, no metastasis, rare in non-white individuals
  - **Plantar:** plantar surface of foot nodular myofibroblastic proliferation, middle-aged individuals, slight male predominance, no metastasis
  - **Penile (Peyronie Disease):** Fibrous proliferation/lesion which causes penile deformities and painful erections and often reports of erectile dysfunction; occurs in white adult males >50
  - **Deep (Desmoid tumor):** myofibroblastic proliferation in deep soft tissue, can cause skeletal muscle atrophy
- Associated with **Familial Adenomatous Polyposis Syndrome** → dramatically increased risk (~1000x general population) → associated with cicatricial variant of fibromatosis
- **IHC**: **Nuclear Beta Catenin+,** SMA+; variable CD117, calretinin expression; Negative for keratin, desmin
- **Molecular:** Testing for APC or CTNNB1 mutations
  - **Familial/FAP → APC**
  - **Sporadic → CTNNB1**







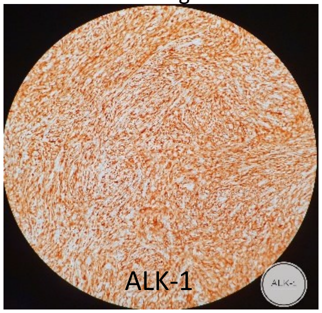
INFLAMMATORY MYOFIBROBLASTIC TUMOR

MORPHOLOGY

- Ovoid to **spindled/stellate myofibroblastic cells** in either a loose **myxoid background**, **sclerotic matrix**, **storiform pattern**, or **fascicles**
- **Myofibroblastic cells:** vesicular nuclei and 1-2 nucleoli, +/- smudgy chromatin, eosinophilic cytoplasm; smudgy chromatin → may have macronucleolus
- **Inflammatory cells present** and variable in number → lymphoplasmacytic predominance

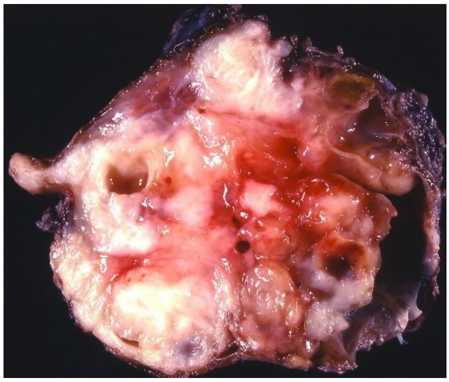
OTHER HIGH YIELD POINTS

- Rare and **occurs in young and old**; **slight female** sex **predilection**
- Low rate of metastasis, recurrence seen in ~40% of cases
- IHC: **Cytoplasmic ALK+** (~50% of cases), SMA+, desmin +/-, Keratin +/-; negative S100P, CD117, EMA, myogenin
- **Molecular**: **ALK rearrangement** (2p23) and promiscuous
  - **Partners**: KLC1, THBS1, EML4, RANBP2, TPM4, ATIX, TPM3, IGFBP5
  - Epithelioid inflammatory myofibroblastic sarcoma
    - **ALK-RANBP2** → most common
  - **ALK-1 expression** → seen in **younger patients**
  - **ALK negative** → consider testing for ROS1, PDGFRB, NTRK3, RET fusions
- Treatment: Complete resection +/- targeted therapy with TKI based on molecular findings

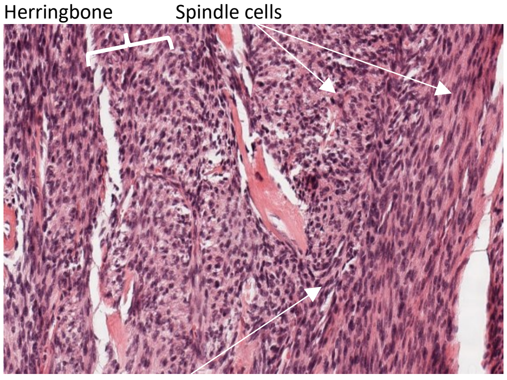


Courtesy of Dr. Raul Perret, MD, MSc

Path Presenter



Courtesy of Dr. Yale Rosen



Path Presenter

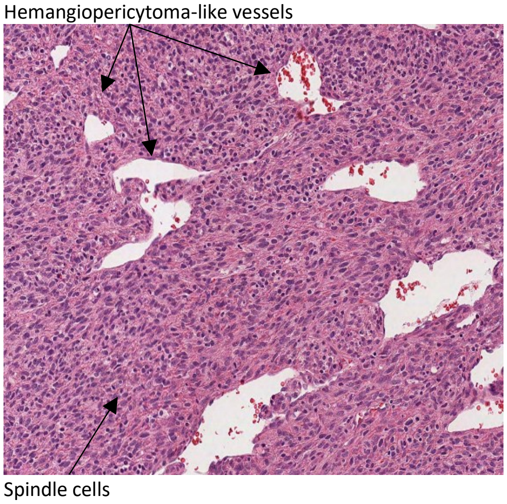
FIBROSARCOMA (ADULT TYPE)

MORPHOLOGY

- **Uniform** and **hyperchromatic fibroblast**-like spindle cells with elongated nuclei and variable cytoplasm
- Spindle cells in a **herringbone pattern** and **intervening collagen fibers**
- **Mitoses** are present

OTHER HIGH YIELD POINTS

- **Malignancy** but **rare** and seen in **middle-aged** to **older adults**
- If subcutis → consider DFSP with fibrosarcomatous transformation
- **Metastatic sites**: **lung** (common), bone, liver
- **Low-grade** → better prognosis; general mortality ~50%
- **Pleomorphism** → think undifferentiated pleomorphic sarcoma (UPS)
- **IHC** (non-specific): SMA+; negative S100, CD34, desmin, EMA, keratins
- No specific or diagnostic molecular abnormality



INFANTILE FIBROSARCOMA (CONGENITAL FIBROSARCOMA)

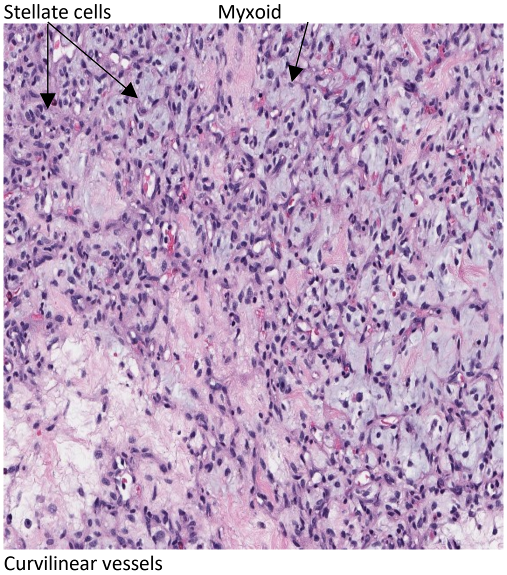
MORPHOLOGY

- Infiltrative **monomorphic spindle cells** in **sheets** or **sweeping fascicles**
- May have a **primitive** (**round cell**) **component** and **brisk mitotic activity**
- Hemorrhage and necrotic foci common
- Hemangiopericytoma-like vessels or myxoid change, or necrosis

OTHER HIGH YIELD POINTS

- **Majority** of cases **occur within 1st year** of life, **slight male** predilection, **nearly 50%** of cases are **congenital**
- Clinically presents as a **rapidly growing solitary mass** +/- skin changes
- Often in distal extremities (most common), head and neck, or trunk
- **Favorable prognosis** (mortality rare) but **recurrence in 50%** of cases
- IHC: **PanTRK positivity** (cytoplasmic)
- **Molecular**: ***ETV6-NTRK3*** → t(12;15)(p13;q25)

Path Presenter



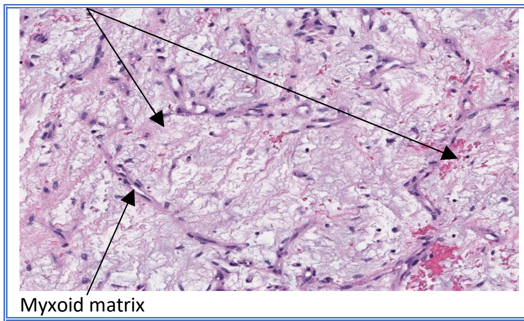
MYXOFIBROSARCOMA

MORPHOLOGY

- Spectrum of morphology and cytologic features based on grade
- **Low grade** → predominant **myxoid component** with **scattered discohesive spindle to stellate cells** with enlarged **hyperchromatic nuclei**; **curvilinear vessels**, **rare mitosis**, no necrosis
- **Intermediate grade** → More **cellularity**, **increased pleomorphism**, more **mitotically active**, presence of **curvilinear vessels**, absence of **necrosis** and sheets of cells
- **High grade** → **Predominantly cellular component** with **fascicle formation** or solid sheets of cells with marked cytologic atypia (**multinucleation**, **bizarre forms**), many **mitotic figures** (and **atypical**), and **necrotic**

OTHER HIGH YIELD POINTS

- **Most common sarcoma** in the **elderly population** with slight M>F
- **Recurrence is common** and unrelated to the grade of the tumor
- **Metastasis**: low-grade → rare; intermediate and high grade → ~40%
- Prognosis dependent on size, grade, margins; overall ~60% 5-year survival
- **Epithelioid variant is aggressive** → majority have recurrence and half will have metastasis
- **IHC**: **nonspecific** and variable CD34, MSA, and SMA; CD34+ in superficial



- **Molecular**: Complex karyotypes but non-specific

Path Presenter

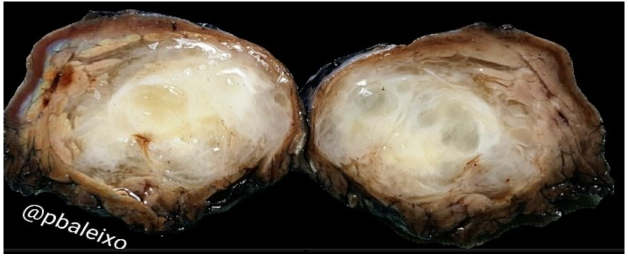
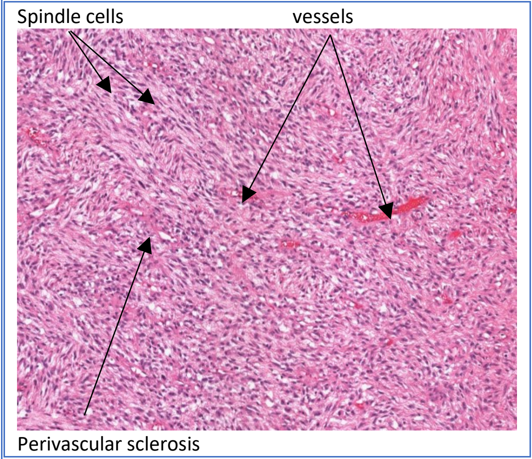


Image credit: Pedro Aleixo @pbaleixo



LOW-GRADE FIBROMYXOID SARCOMA

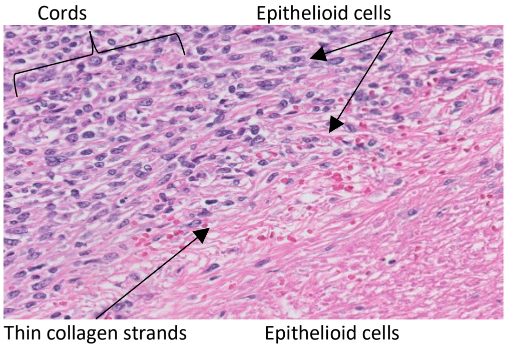
MORPHOLOGY

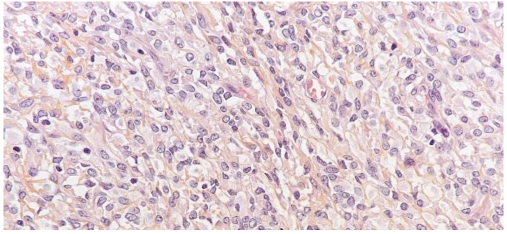
- **Bland spindle cells** with **indistinct cytoplasm** in **small fascicles** and **whorled patterns** and **fibrocollagenous** and myxoid component
- **Myxoid foci** → arcades of vessels +/- perivascular sclerosis

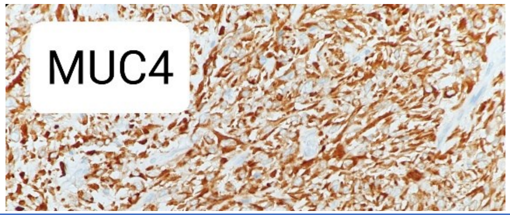
OTHER HIGH YIELD POINTS

- **Malignant but** has **indolent** nature
- Wide variation in age and ~20% occur in pediatrics (<18 years old)
- IHC: **MUC4+**, +/- DOG1; negative Claudin-1, EMA, CD34, p40, keratins, S100
- **Molecular:** Chromosomal translocations
  - ***FUS-CREB3L2* fusion → t(7;16)(q33;p11) most common**
  - ***FUS-CREB3L1* fusion → t(11;16)(q11;p11)**

Path Presenter







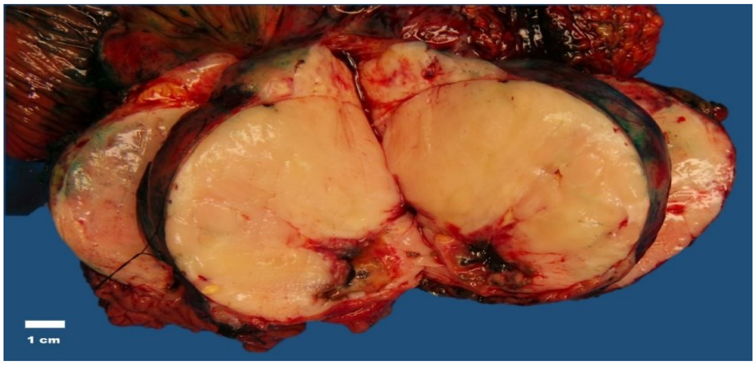
SCLEROSING EPITHELIOID FIBROSARCOMA

MORPHOLOGY

- **Small** to **medium-sized epithelioid cells** with **variable** clear to eosinophilic **cytoplasm** and **bland ovoid nuclei**
- Epithelioid cells **arranged** in **chains**, **cords**, or **nests reminiscent of a pseudoalveolar** or **pseudoacinar** appearance
- **Dense hyalinized and sclerotic matrix** with thin collagen strands

OTHER HIGH YIELD POINTS

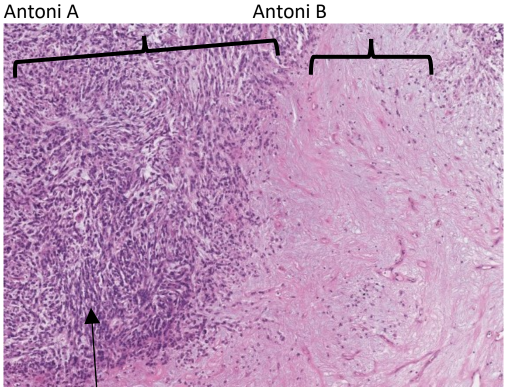
- Rare, **occurs in middle-aged** or **older individuals** in **lower limbs/girdles**
- **Prognosis** → poor, **metastasis to CNS**, bone, lung/pleura
- **IHC**: **MUC4+**, +/- EMA; negative for keratins, SATB2, S100, SMA, CD34
- **Molecular** → ***EWSR1-CREB3L1* fusions**

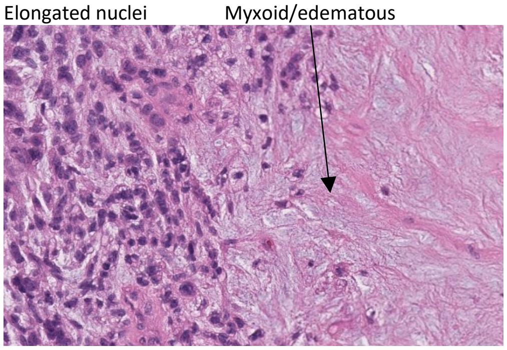


Credit: Raul Perret, MD, MSc @kells108

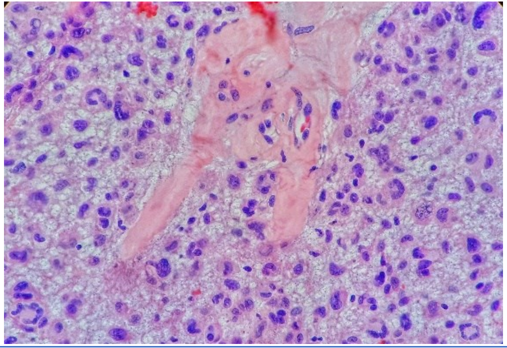
Path Presenter

NERVE SHEATH TUMORS





Epithelioid Schwannoma



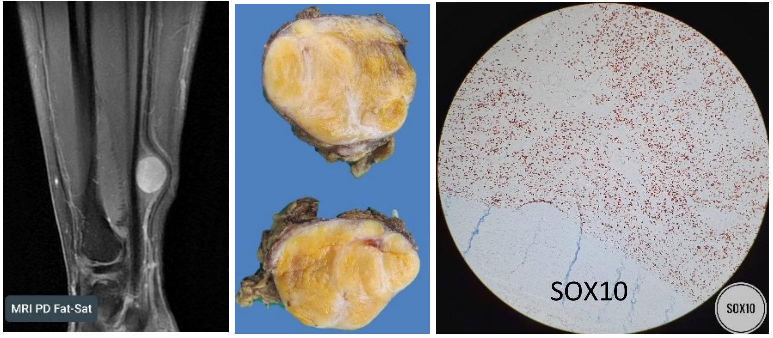
SCHWANNOMA (NEURILEMMOMA)

MORPHOLOGY

- **Antoni A: spindle cells** arranged in **small fascicles** (loose or tight) with **whorling and nuclear palisading → Verocay body**
- **Antoni B: Ovoid to spindle cells suspended** in a **myxoid/edematous matrix**, often has **cystic changes** with inflammatory infiltrate
- **Spindle cells** (Schwann cells) have elongated or “carrot-like” nuclei +/- nuclear inclusions with no significant atypia and cytoplasm with indistinct borders; **Nuclear atypia → degeneration** (ancient change)
- Can have **metaplastic changes** → bone formation, calcifications
- Epineural capsule surrounds the entire lesion

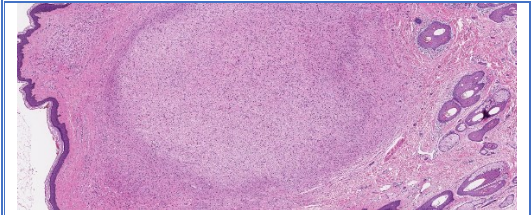
OTHER HIGH YIELD POINTS

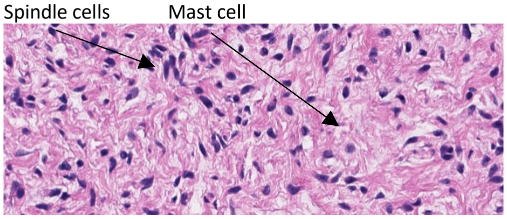
- **Benign, painless neoplasm** occurring in **head/neck**, and **extremities**
- Occurs in **all ages**, no sex predominance, **majority** are **sporadic**
- **Syndromic association → multiple meningiomas** (most common), **NF2**, **schwannomatosis**, NF1 (extremely rare)
- May be seen in other organs → GI, renal, or pancreaticobiliary
- Many **morphologic variants:**
    - Ancient, cellular, plexiform, epithelioid, pseudoglandular, neuroblastoma-like, reticular/microcystic-like
- **IHC:** Positive for S100, SOX10, H3K27me; negative for EMA, CD34, GLUT1;
    - **Epithelioid variant → loss of INI1** in ~50% of cases
    - **Retroperitoneal, posterior mediastinal, GI → GFAP** and **CKAE1/AE3 +**



Credit: Raul Perret, MD, MSc @kells108

Path Presenter





NEUROFIBROMA

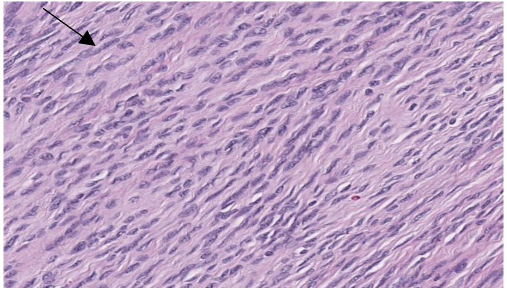
MORPHOLOGY

- Spindle cell tumors composed of **perineural-like cells**, **fibroblasts**, and **Schwann cells**
- **Cellularity** is **variable** and has **interspersed mast cells**

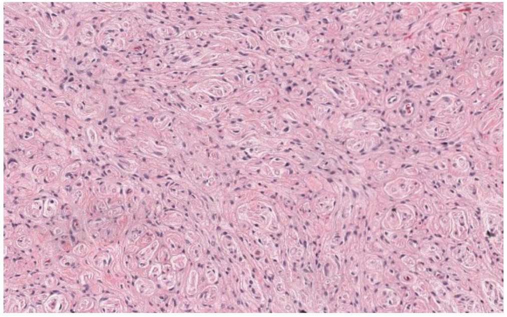
OTHER HIGH YIELD POINTS

- **Most common peripheral nerve sheath tumors**, majority (~90%) are sporadic
- Wide age range with no sex predominance, **slow-growing mass**
- **Factors predisposing** to **malignant** transformation
    - **NF1 patients**
    - **Plexiform and intraneural** → most common precursor to **MPNST**
- **IHC:** Positive for S100 and SOX10, CD34 (fibroblasts), EMA (perineural cells); intact H3K27me

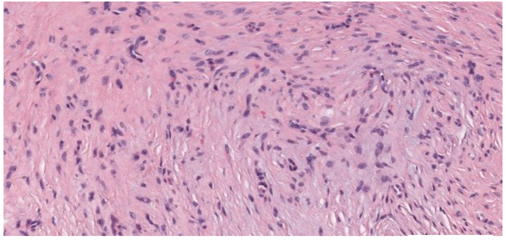
Path Presenter



Intraneural type



Sclerosing subtype



[Path Presenter]

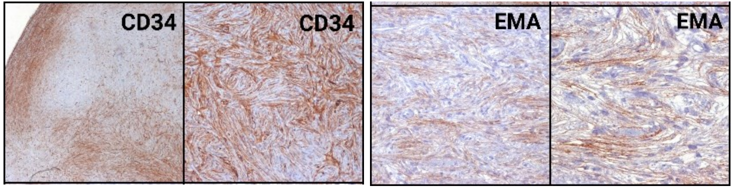
PERINEURIOMA

MORPHOLOGY

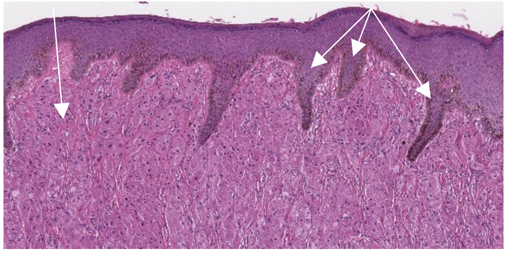
- Cytologically **bland spindle cells** with **variable nuclei** (round to wavy) **arranged** in **various patterns** (fascicular, lamellar, storiform, whorling)
- **Myxoid** to **collagenous stroma**
- **Unencapsulated**

OTHER HIGH YIELD POINTS

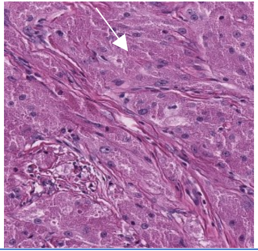
- Rare **benign neoplasm** arising from **perineural cells**
- Generally, **no sex predominance** and occurring in **adults**
  - **Sclerosing variant** → **male** predominance
- **Clinically**: **slow-growing**, **painless mass** seen in extremities or trunk
- **Morphologic variants**:
  - **Intraneural:** Bland perineural cells with characteristic "onion-skin" (concentric layers) around nerve axons → expanded nerve tissue
  - **Sclerosing:** Epithelioid to plump spindle cells arranged in a trabeculae, cords, or whorled pattern, hyalinized stroma with blood vessels with thin walls
  - **Reticular:** Thin fusiform spindle cells with lace-like anastomosis, pseudocystic spaces and conspicuous myxedematous stroma
  - **Plexiform:** Serpiginous pattern of perineurioma
- **IHC:** Positive for **GLUT1**, **claudin1**, **EMA**; variable CD34; negative for MUC4, SMA, keratins, desmin, and S100
- **Molecular**:
  - **22q abnormalities (most common)**, Less commonly→ del 17q
  - **Sclerosing perineurioma** → **Deletions** or **rearrangements** of **10q**
  - **Intraneural perineurioma** → **TRAF7 mutations**



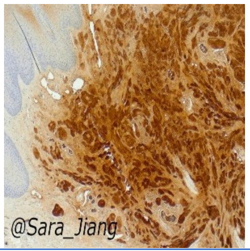
Credit: Raul Perret, MD, MSc @kells108



Granular cytoplasm



S100 IHC



GRANULAR CELL TUMOR

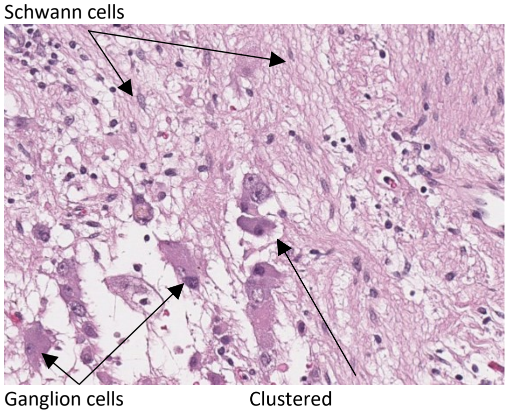
MORPHOLOGY

- **Polygonal cells** with **granular eosinophilic cytoplasm** arranged in **cords**, **nests**, and **sheets** in a **collagenous stroma**
- **Overlying epithelium** → **pseudoepitheliomatous hyperplasia**

OTHER HIGH YIELD POINTS

- **Benign** tumor cells of **Schwannian origin**
- **Most common: middle-aged females**, high incidence →**Black women**
- **Clinically:** slow-growing mass/plaque/nodule in head and neck
- If **malignant** → **~50% metastasize** and 30% recur
- **Adverse prognosis:** metastasis, recurrence, size > 5cm, older age
- IHC: Positive for **S100**, **TFE3**, **SOX10**, CD68, inhibin, MITF, calretinin; negative for ALK, GFAP, HMB45, NF, SMA, desmin, myogenin
- EM: **Rudimentary intercellular junctions**, **pleomorphic secondary lysosomes**

[Path Presenter]



GANGLIONEUROMA

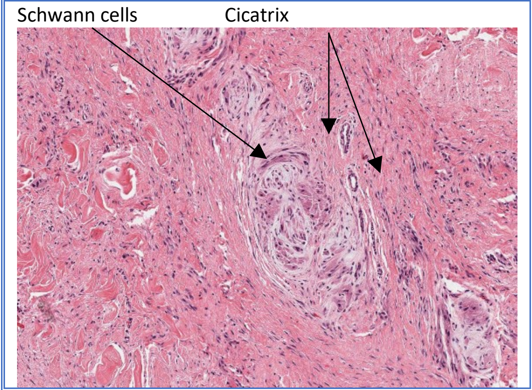
MORPHOLOGY

- Monotonous **spindled Schwann cells** with **elongated/wavy nuclei** arranged in **fascicles or no specific pattern**
- **Collagenous stroma**
- **Ganglion** cells arranged singly, in small nests or clusters

OTHER HIGH YIELD POINTS

- Rare, **benign tumor** from **neural crest**, sympathetic/peripheral nerves
- Usually seen in **young adults** with no sex predilection
- Most common locations: **posterior mediastinum**, **retroperitoneum**
- Large tumors can **secrete catecholamines** → **sweating** and **diarrhea**
- **IHC**: positive **S100**, **NF** (Schwann, ganglion), **synaptophysin** (ganglion)

Path Presenter



TRAUMATIC NEUROMA

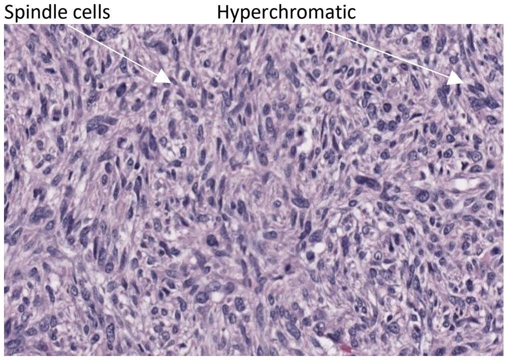
MORPHOLOGY

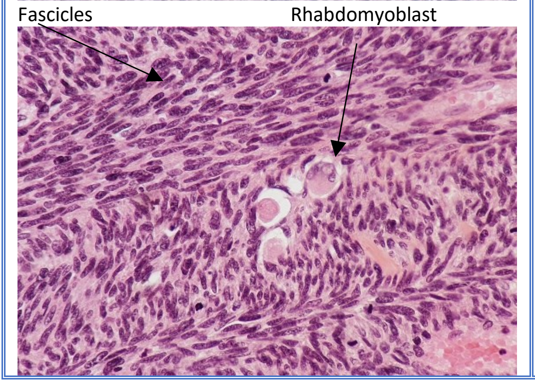
- Hyperplastic **proliferation** of **cytologically bland spindled Schwann cells** with elongated nuclei and eosinophilic cytoplasm with indistinct borders
- **Unencapsulated nerve fibers** arranged in **irregular fascicles** in **cicatrix**

OTHER HIGH YIELD POINTS

- Occurs after **trauma** → amputation, injury, etc
- **Clinically** presents as a **painful mass**
- **IHC**: Not generally needed for diagnosis

Path Presenter





MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST)

MORPHOLOGY

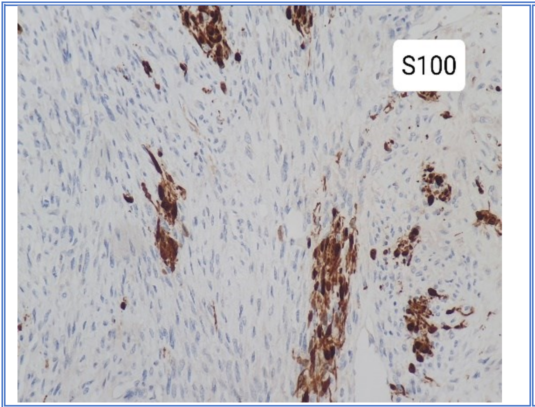
- **Proliferation** of variably cellular **hyperchromatic uniform spindled cells** with pale cytoplasm arranged in fascicles, whorls, herringbone
- Background stroma: **collagenous to myxoid** and is **vascular**
- May have a primitive component

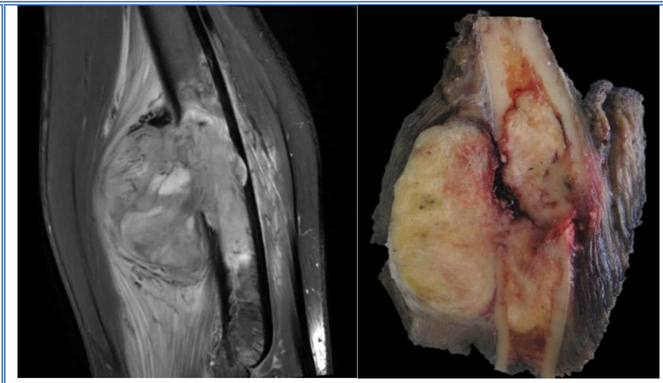
OTHER HIGH YIELD POINTS

- **Patients with NF1:** present **younger age** with **male** predominance
- Heterologous differentiation may be present
- Majority arise from **major nerves** → **Sciatic** (**most common**)
- **Poor prognosis**: **metastasis in ~60%** and recurrence in almost 50%
- **Adverse factors** → central location, >5 cm, recurrence, high-grade
- IHC: **Diffuse loss** of nuclear **H3K27me**; positive for **SOX10**, **S100**; +/- CD34, GFAP; negative for SMA, desmin, MART-1, and keratins
- **Molecular**: Numeric chromosomal abnormalities

Malignant Peripheral Nerve Sheath Tumor with Rhabdomyoblastic Differentiation (Malignant Triton Tumor)

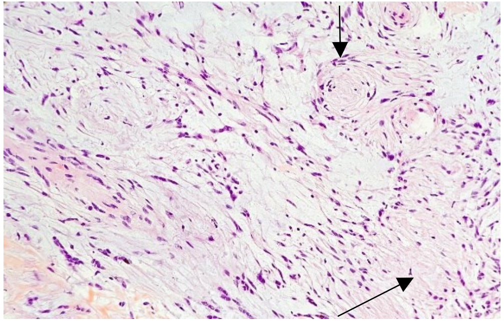
- **Associated with NF1**
- **Rhabdomyoblasts** (mature with abundant eosinophilic cytoplasm) scattered throughout MPNST
- May show epithelial, chondroid or osteoid differentiation
- **IHC: positive for Desmin, Myogenin, and MyoD1**
- **Poor prognosis**

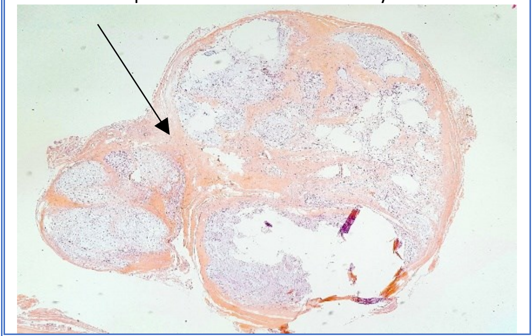




Credit: Raul Perret, MD, MSc @kells108

Path Presenter


Spindled cells
Whorls
Verocay-like bodies


Fibrous septae

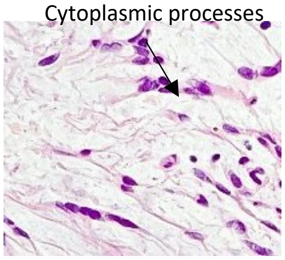
NERVE SHEATH MYXOMA

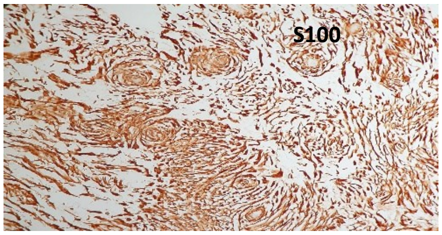
MORPHOLOGY

- **Lobular proliferation** of **epithelioid to spindled cells** and suspended in a **myxoid matrix**
- Often have **interconnecting networks**, **syncytial nests**, **verocay-like bodies**, and **ring-like structures**
- Lobules are separated by dense **fibrocollagenous septae**
- Cells **lack atypia** and without **mitosis**

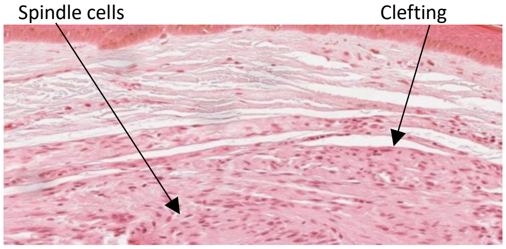
OTHER HIGH YIELD POINTS

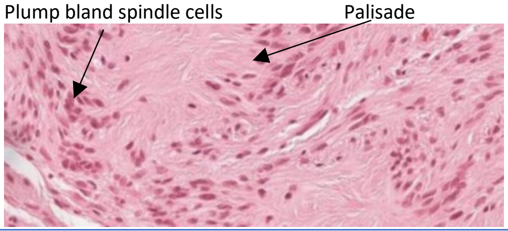
- **Extremely rare tumor**, mostly seen in adults **in 3rd decade**
- Most common location is **hands/fingers** or **pretibial skin**
- Presents as a **painless**, **slow-growing** mass
- Recurrence rate in half of cases
- **IHC**: positive for **S100** (image below), **GFAP** (in most)


Cytoplasmic processes



Photos courtesy of Raul Perret, MD, MSc @kells108


Spindle cells
Clefting


Plump bland spindle cells
Palisade

SOLITARY CIRCUMSCRIBED NEUROMA (PALISADED ENCAPSULATED NEUROMA)

MORPHOLOGY

- **Plump bland spindle** cells arranged in **interlacing fascicles** with a **collagenous** stromal background and "**clefting**"
- Palisading may be subtle or obvious
- Degenerative changes → often seen hyperchromasia

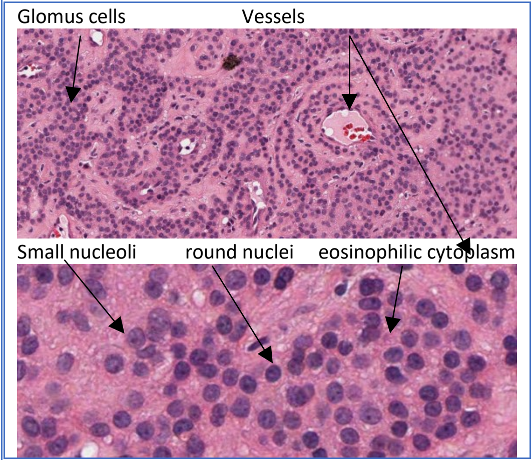
OTHER HIGH YIELD POINTS

- **Benign** tumors arising in **middle age to older adults** with no sex predilection and found on the **head and neck**
- Most common cutaneous sites → **lips**, **nose**, **forehead**
- Most common non-cutaneous site → **oral mucosa**
- IHC: Positive for **S100 protein**, SOX10 (Schwann cells), NF (axons)
- **No association** to **NF1** or **MEN2B syndromes**

Path Presenter

8. BONE AND SOFT TISSUE PATHOLOGY

PERIVASCULAR TUMORS



GLOMUS TUMOR

MORPHOLOGY

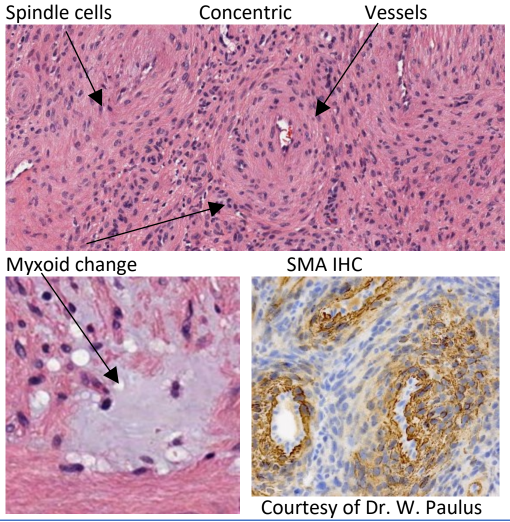
- Proliferation of **small nests** of **glomus cells** which have **round nuclei** with single **small nucleolus** and **amphophilic to eosinophilic cytoplasm**
- Cells organized around **vascularized hyalinized** to **myxoid stroma**
- Absence of necrosis

OTHER HIGH YIELD POINTS

- **Mostly young adults**; **female predominance** in **subungual tumors**
- **Clinically**: small **red-blue painful nodule** on **stimulation** & **cold temperatures**
- **IHC**: positive for **SMA**, **caldesmon**, and variable TLE1
- **Molecular**: NOTCH gene rearrangements

Path Presenter

Courtesy of Dr. S. Koch



Courtesy of Dr. W. Paulus

MYOPERICYTOMA

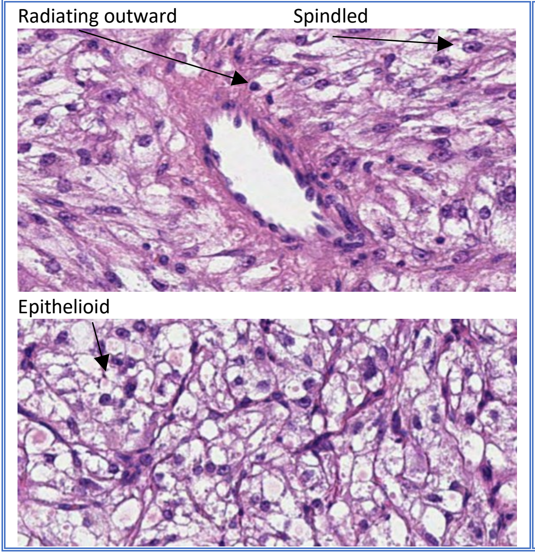
MORPHOLOGY

- **Uniform plump** ovoid to **spindle cells** with **cytologically bland nuclei** and have **concentric growth** pattern **around thin-walled blood vessels**
- May have **degenerative changes** → **myxoid stroma**, **atypical nuclei**, **hemorrhage**, **hyalinization**, infarction, **metaplastic bone formation**
- Mitotic activity is rare

OTHER HIGH YIELD POINTS

- Usually seen in **middle-aged adults** with **male** predominance
- Clinically presents as a **single**, **painless**, **slow-growing** mass on the dista**l** **lower extremities** in deep soft tissue
- Unlikely to have a local recurrence
- IHC: Positive for h-caldesmon; negative for CD31/CD34, keratins
- **Molecular**: Alteration in **PDGFRB**

Path Presenter



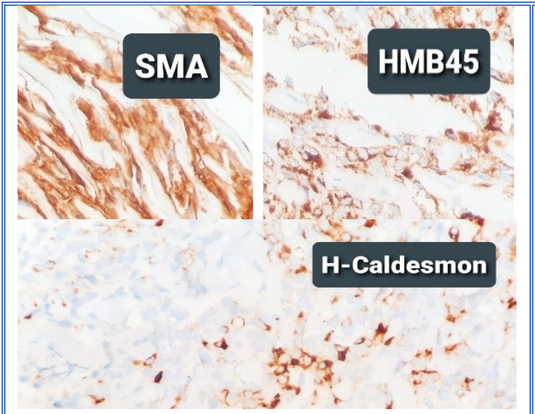
PERIVASCULAR EPITHELIOID CELL TUMOR (PEComa)

MORPHOLOGY

- **Epithelioid** to **spindled cells** with round to oval nuclei and lightly **eosinophilic cytoplasm** and arranged in **nests**, **sheets**, or **trabeculae** and **radiate outward from vessels**
- Few multinucleated giant cells may be seen
- Can have melanin pigment

OTHER HIGH YIELD POINTS

- Rare tumors occurring **mostly** in **middle-aged females**
- **Can arise anywhere** but uncommon in bone, skin, and extremities
- Clinically presents as a **painless mass** +/- site-specific symptoms
- **Morphologic variants**
  - **Fibroma-like** PEComa → **associated with TS**
  - **Sclerosing PEComa** → **not** associated with **TS**
- Features with risk of malignant behavior (**Folpe** criteria)
  - **High risk:** >5 cm, cellular, high nuclear grade, mitoses, necrosis, vascular invasion, infiltrative growth pattern
  - **Likely benign:** <5cm in size and <2 high-risk features

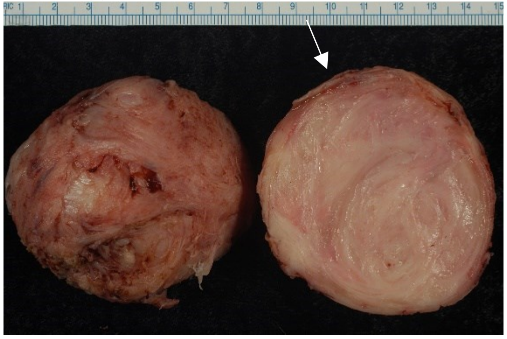


IHC courtesy of Dr. Raul Perret, MD, MSc (@kells08)

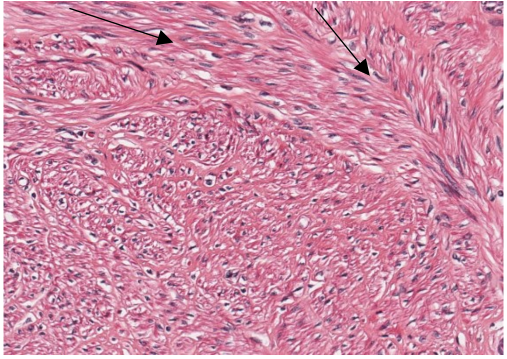
  - **Uncertain malignant potential**: size 5 cm or greater, no other high-risk features, or multinucleated giant cells/or pleomorphism only
  - **Malignant:** Two or more high-risk features
- **IHC**: **Myomelanocytic phenotype**→ positive for **HMB-45**, MiTF, MART-1 **SMA**, desmin, caldesmon
  - **HMB-45** and **SMA most sensitive** markers
- **Pathogenesis**: **TSC2 deletion → mTOR pathway activation**
- **Molecular**:
  - **TSC2 deletion-related** → mTOR pathway activation
  - **Non-TSC2 related → TFE3 mutations** or **SFPQ-TFE3 fusion**

Path Presenter

SMOOTH MUSCLE TUMORS



Courtesy of Dr. Ed Uthman (@euthman)



LEIOMYOMA

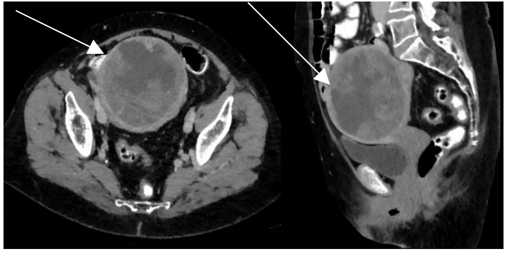
MORPHOLOGY

- **Uniform spindle cells** in **short fascicles** or **aggregates**
- Spindle cells have "**cigar-shaped**" **nuclei** and **eosinophilic cytoplasm**
- **No pleomorphism**, significant mitotic activity or necrosis

OTHER HIGH YIELD POINTS

- **Older patients**, no sex predominance (except pelvic tumors, F>>M)
- Mitotic rate and relation to sex and location
- Gross examination: Tan-white, whorled cut surface
- **Deep tissues:**
  - <1mitosis / 50HPF → Benign leiomyoma
  - 1 to 5 /50HPF → Smooth muscle tumor of uncertain malignant potential (STUMP)
- **Retroperitoneal/Pelvic in women**
  - <5mitosis / 50HPF → Benign leiomyoma
  - 5 to 10 /50HPV → STUMP
- **Retroperitoneal/Pelvic in men**
  - <1mitosis / 50HPF → Benign leiomyoma
  - 1 to 5 /50HPV → STUMP
- **IHC**: Positive for MSA, SMA, desmin, h-caldesmon
  - Female pelvic/retroperitoneal tumors positive for WT-1, ER, and PR
- **Molecular**: Genetic heterogeneity
  - **EWSR1-PBX3** or **KAT6B-KANSL1 fusions → retroperitoneum**
  - PLAG1 or HMGA2 gene aberrations

Path Presenter



Radiology courtesy of Dr. Hellerhoff

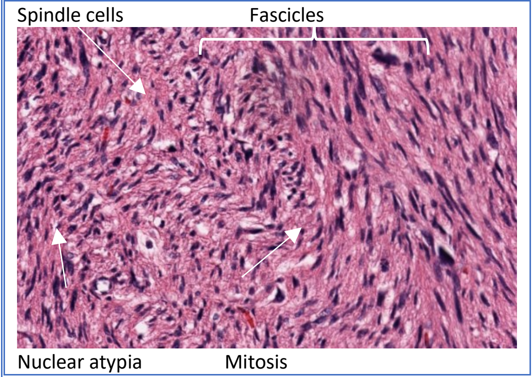
LEIOMYOSARCOMA

MORPHOLOGY

- **Spindle cells** with **intersecting fascicles** with **infiltrative borders**
- Spindle cells have "**cigar-shaped**" **nuclei**, **atypia**, **mitoses** and **necrosis**

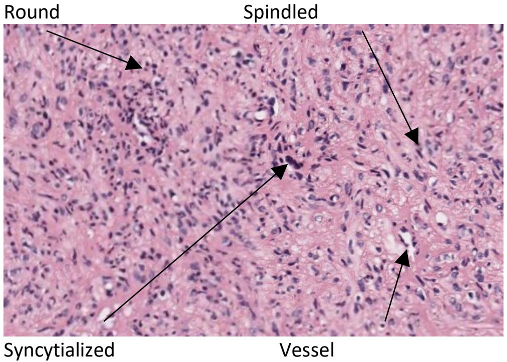
OTHER HIGH YIELD POINTS

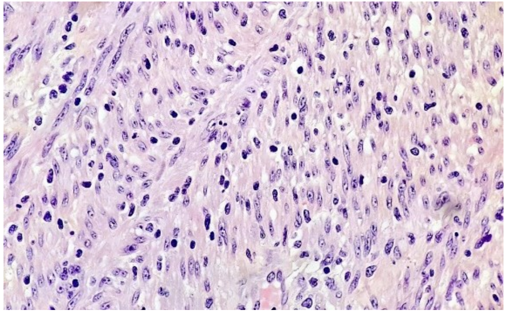
- **Malignant tumor**, older adults, no sex predilection (**pelvic → F>>M**)
- **Sites**: retroperitoneum, inferior vena cava, lower extremities, viscera
- **Poor prognosis** and **majority have metastasis**
  - **Most common** site is the **lung**
  - **Hematogenous route of metastasis**



- **Morphologic variants:**
    - **Pleomorphic**: marked pleomorphic tumor cells resembling undifferentiated pleomorphic sarcoma
    - **Myxoid:** low grade, abundant myxoid stroma
    - **Epithelioid:** small cells with scant eosinophilic cytoplasm or large eosinophilic cells with macronucleoli arranged in nests and sheets
- **IHC**: **positive** for **SMA**; +/- caldesmon and desmin; negative p63, CD34, HMB-45, MART-1, CD117, ALK1, S100
- **Molecular**: **Complex karyotypes**

Path Presenter





Credit: Raul Perret, MD, MSc (@kells108)

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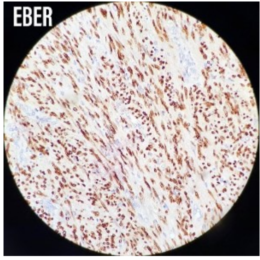
EBV-ASSOCIATED SMOOTH MUSCLE TUMOR

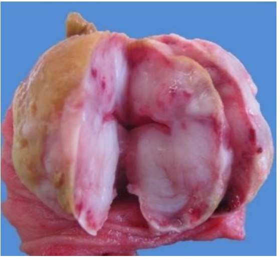
MORPHOLOGY

- Tumor cells are variable in morphology
    - **Round (primitive) to spindled** and may be **syncytial**
- Tumor cells form **storiform fascicles** or **faint fascicles**
- **Rarely pleomorphic** and **necrosis** typically **absent**
- **Mitotic activity is high** but **lacks atypical forms**
- **Prominent vascularity** is seen

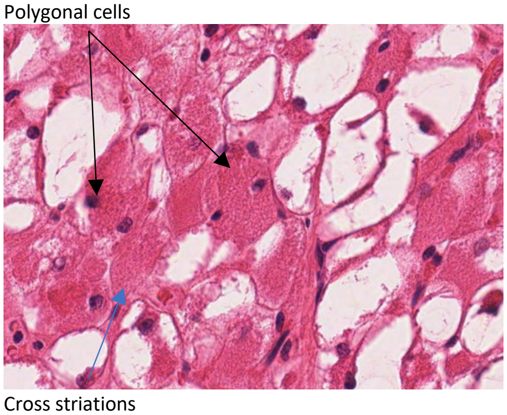
OTHER HIGH YIELD POINTS

- **Very rare indolent tumor** but commonly seen in **immunosuppressed patients**, with **majority** having **had** a **renal transplant**
- Average age is **50 years old** and **no sex predilection**
- Most common in **larynx** in the **true vocal cords**
- **IHC**: **positive** for **SMHC, MSA, SMA, p53**, and **h-caldesmon**; negative for p63, S100, SOX-10, HMB-45, TLE1, EMA, CD99, and panCK
- **In situ hybridization: EBER strongly positive** and diffuse in nucleus





SKELETAL MUSCLE TUMORS



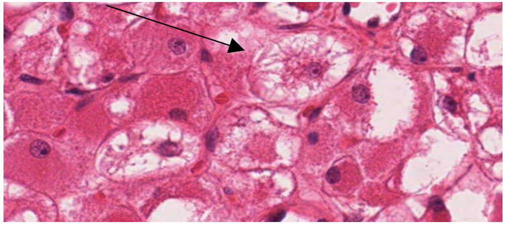
RHABDOMYOMA

MORPHOLOGY

- Large **polygonal tumor cells** with **central or eccentric nuclei**, **finely granular** eosinophilic **cytoplasm**, arranged in **small nests** and **sheets**
- Cytoplasm often has **cross striations** and +/- inclusions
- **Delicate capillary** network
- Absence of necrosis and mitosis

OTHER HIGH YIELD POINTS

- Predominantly occur in the **head** and neck of **middle-aged men**
- Clinically presents as a **painless**, **slow-growing** mass
- May be **multifocal**, **seen in ~20%** of cases
- About **60% of cases do not have** a **recurrence**
- Other Rhabdomyoma types:



- ➢ **Cardiac type:** hearts of infants and children, associated with TSC, has “spider web cells”
- ➢ **Fetal type**: head and neck and occur at any age
- **IHC**: positive for **MYOD1**, **desmin**, myogenin; negative for CD163, PAX-8, TFE3, keratin, CD68, and synaptophysin

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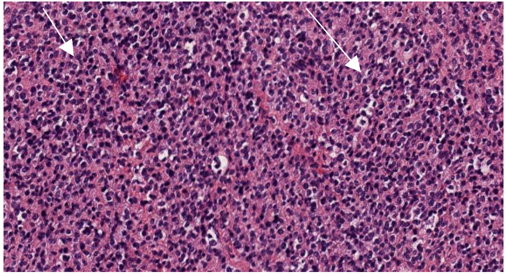
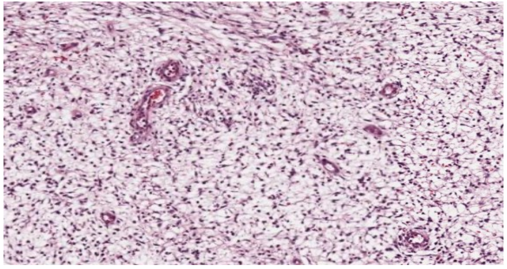
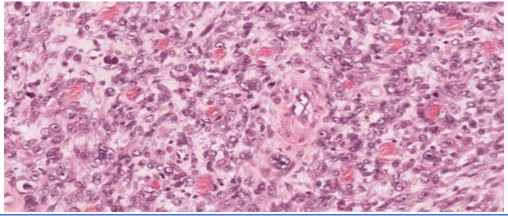


Botryoid type



Anaplastic



EMBRYONAL RHABDOMYOSARCOMA

MORPHOLOGY

- Tumor cells with **variable morphology** (spindle, stellate, ovoid) with **hyperchromasia**
- **Variable cellularity** and described as “**marbled**” **appearance** → **alternating cellular** and **hypocellular** foci
- Tumor cells may show **rhabdomyoblastic differentiation**→ **eccentric nuclei** and prominent **eosinophilic cytoplasm** +/- **striations**
- Other tumor cells can be described as “**tadpole cells**” or “**strap cells**”
- **Mitoses frequently seen** and necrosis is variable

OTHER HIGH YIELD POINTS

- **Most common sarcoma in children** in first decade, **slight male predominance**
- Often occur in the **head and neck** region or **genitourinary system**
- **Morphologic variants**:
  - ➢ **Botryoid type: densely cellular layer** below cambium layer (epithelial surface) and separated by **hypocellular zone**; presents as a **grape-like mass** from the **vagina** or **nasal cavity**
  - ➢ **Anaplastic type:** pleomorphic nuclei with atypical mitotic figures
- **Prognosis greatly affected** by stage, age, location, and histologic grade
- IHC: **Positive MYOD1 and Myogenin (nuclear)**, **desmin**; +/- keratin, SMA
- **Molecular**:
  - ➢ **Complex karyotypes** → gains of chromosomes in 2, 8, 12, 14
  - ➢ Characteristic **loss of heterozygosity** of **11p15.5**
  - ➢ **Absence of PAX7-FOXO1** and **PAX3-FOXO1 fusions**

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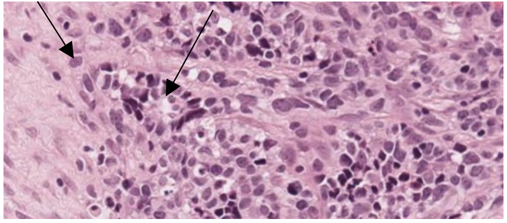
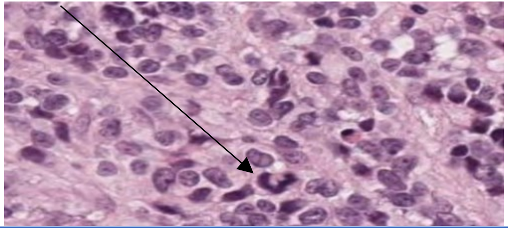


Atypical mitoses



ALVEOLAR RHABDOMYOSARCOMA

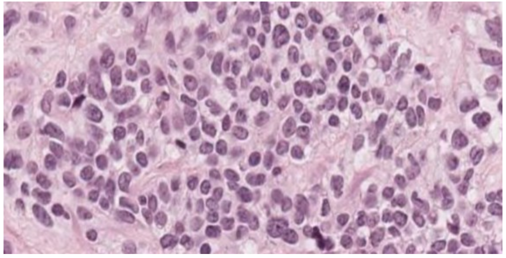
MORPHOLOGY

- Sheets of **primitive monomorphic round cells** (“round blue cell”) with **hyperchromatic nuclei** and a few with **small nucleoli** and **scant cytoplasm**
- Dense **variably-thick fibrous septa** separate nests and sheets of round cells imparting a **“pseudoalveolar” pattern**
- **Necrosis is seen**, especially within central parts of nests/sheets of cells
- **Mitotic activity** is **conspicuous**
- Multinucleated cells, peripherally located nuclei → **“wreath-like”** cells

OTHER HIGH YIELD POINTS

- **Second most common type** of rhabdomyosarcoma and **seen in adolescents** and **young adults** (M=F)
- Seen in **deep tissue of the extremities** but can be seen in the **head and neck**, **paraspinal**, **retroperitoneum**, and **perineal areas**
- **Clinically**: **rapidly-growing mass** and symptoms depend on location
- Morphologic variant → **Solid-type** which **lacks pseudoalveolar pattern**

Scant cytoplasm



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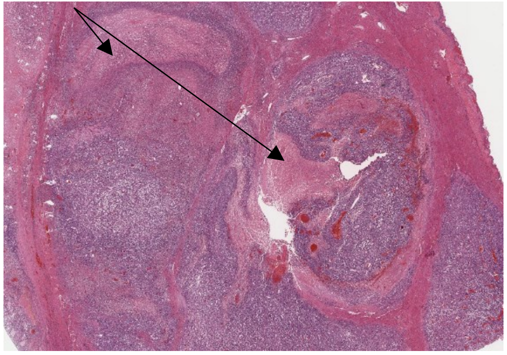
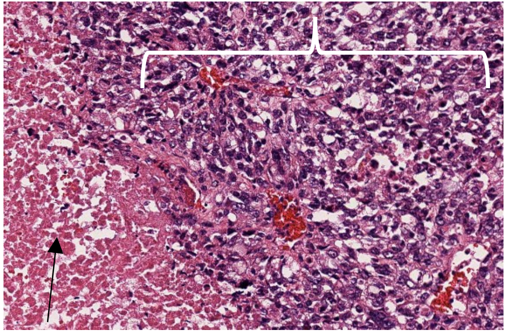
- **Prognosis**: worse compared to embryonal type rhabdomyosarcoma
- Clinically **high stage at presentation**
- **IHC**: **positive for MyoD1**, **Myogenin**, **MSA**, **desmin, ALK**; variable keratin (patchy), synaptophysin, CD56, CD99 expression
- **Molecular**: Two main recurrent chromosomal translocations
  - **Most common: PAX3-FOXO1 → t(2;13)(q35:q14)**
  - **PAX7-FOXO1 → t(1;13)(q36:q14)**
  - Alternative fusions seen in ~20% and negative by RT-PCR → consider INO80D, NCOA1 as possible partners; some cases may be truly lacking a fusion
  - **Fusion negative is more common** in **mixed embryonal/alveolar** or **solid** growth **patterns**

Geographic necrosis



Pleomorphic rhabdomyoblasts



Necrosis

PLEOMORPHIC RHABDOMYOSARCOMA

MORPHOLOGY

- Tumor composed of **significantly pleomorphic rhabdomyoblasts**, which have a variety of morphology
- **Unlikely to see cross-striations** in any cell
- **Three morphologic patterns**:
  - **Round cell pattern**: pleomorphic rhabdomyoblasts in clusters and medium-round cells in the background
  - **Classic pattern:** pleomorphic rhabdomyoblasts in sheets
  - **Spindle cell pattern:** pleomorphic spindle cells in storiform arrangement, rarely fascicular pattern, few pleomorphic rhabdomyoblasts seen throughout
- **Mitoses are conspicuous** and have **atypical forms**
- **Necrosis** is typically seen **in a geographic pattern**

OTHER HIGH YIELD POINTS

- Mostly seen in **middle-aged adults**
- **Clinically**: **lower extremity** deep **soft tissue mass** → particularly **thigh**
- **Very aggressive high-grade sarcoma** with early metastasis
- **Prognosis is poor** and **mortality hig**h (~70%)
- **IHC**: **positive** for **MyoD1** (strong), desmin, actin; variable keratins; negative for S100, CD45, melanocytic markers
- Molecular findings are non-specific, most have complex karyotypes

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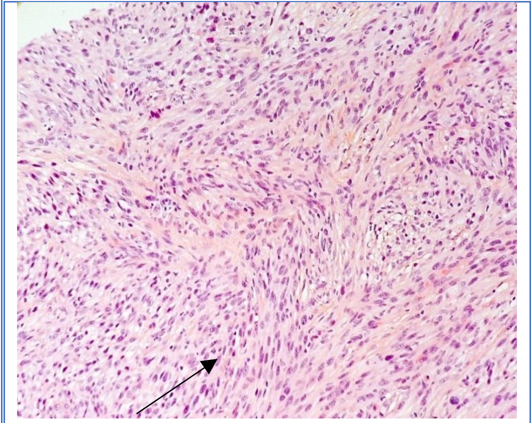


spindle cells with hyperchromatic nuclei

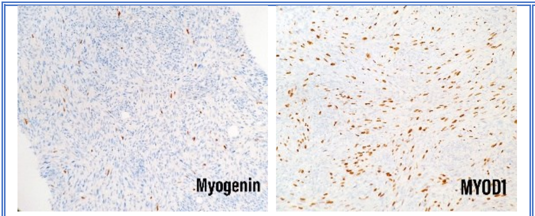
SPINDLE CELL RHABDOMYOSARCOMA

MORPHOLOGY

- **Uniform spindle cells** with **hyperchromatic nuclei** that are **ovoid or wavy** and have **variable nucleoli** and **scant eosinophilic** to **amphophilic cytoplasm**
- **Spindle cells** usually in **fascicular pattern** but can have foci of herringbone or storiform patterns
- Uncommon to have necrosis

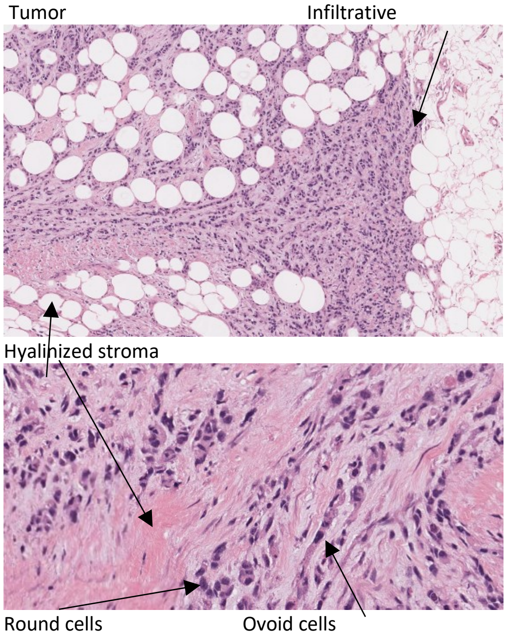
OTHER HIGH YIELD POINTS

- Seen in both **children** (**first decade**) and **adults** (3rd decade)
- Location is variable based on age
  - **Children: paratesticular**; **Adults**: 50% in **head and neck**
- Clinically presents as a **painless mass** that is deep
- Prognosis is dependent on the age group
  - **Children: good if at low stage,** 95% survival at 5 years
  - **Adults: Metastasis, recurrence in 50%; Metastasis: lungs, lymph node**



Credit: Raul Perret, MD, MSc @kells108

- **IHC**: **Positive** for **MyoD1** and **Myogenin** (both nuclear), **Desmin** (diffuse cytoplasmic), **Actin**; negative for keratins, caldesmon, S100, CD34, TLE1, and beta-catenin
- **Molecular**: No genetic findings as seen in alveolar or embryonal RMS
  - **Spindle cell type:** recurrent **MYOD1 mutations**
  - **Infantile/congenital spindle cell RMS:** few reports of NCOA2 and VGLL2 rearrangements



SCLEROSING RHABDOMYOSARCOMA

MORPHOLOGY

- Tumor cells are **variable in morphology**, **primitive**, and range from **round-ovoid to spindled cells** with **eosinophilic to clear cytoplasm** in a nested or cord pattern
- **Hyalinized collagenous stroma** → mimics vascular spaces or osteoid
- **Mitoses are common**, peripheral edge of tumor shows infiltration

OTHER HIGH YIELD POINTS

- Rare and **variable age at presentation**, **strong male predominance**
- Clinically presents as a **deep, painless mass** in the **extremities**
- **Prognosis**: **poor and 50% will have metastasis** and recurrence
  - **MYOD1 mutation → worst prognosis**
- **IHC**: **positive for MyoD1 (diffuse)**, **Myogenin** (focal), and **Desmin** (perinuclear dot-like), +/- SMA; negative for keratins, SATB2, S100, CD31,and CD34
- **Molecular**: Lacks genetic findings seen in embryonal and alveolar type
  - Recurrent MYOD1 mutations and/or PIK3CA mutations
  - MYOD1 suggestive of common pathogenesis for Sclerosing and spindle cell RMS

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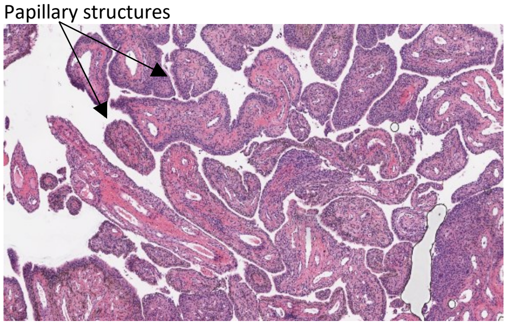
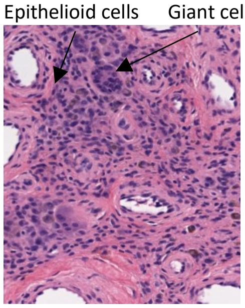
FIBROHISTIOCYTIC TUMORS





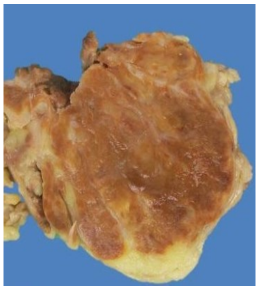


Image Credit: Raul Perret, MD, MSc @kells108

TENOSYNOVIAL GIANT CELL TUMOR (DIFFUSE TYPE)

MORPHOLOGY

- **Large epithelioid cells** with nuclei that are **round to ovoid** and **eccentrically** located with **conspicuous nucleoli** and **ample eosinophilic**
- **Osteoclast-like giant cells**, **macrophages**, **hemosiderin** present
- **Mitotic** figures **frequently seen**
- Lesion is **well-circumscribed**

OTHER HIGH YIELD POINTS

- **Rare benign tumor** with **wide age of occurrence**, **slight female predominance**
- **Most common** in **intraarticular spaces → majority in the knee** (~80%), and hip (10-15%); can be **extraarticular as well → knee still most common**
- Clinically **presents as a painful mass** that has been **present for years**, and **limits the range of motion** of affected joint; body fluid (synovial) often shows hemorrhagic effusion with inflammatory cells
- **Prognosis**: Recurrence/relapse is high (~50%)
  - **Very rare transformation to malignancy** → seen in **radiation exposure**
  - Rare metastasis
- **IHC**: Negative for H3.3 G34W
- **Molecular**: **COL6A3-CSF1** fusions commonly seen

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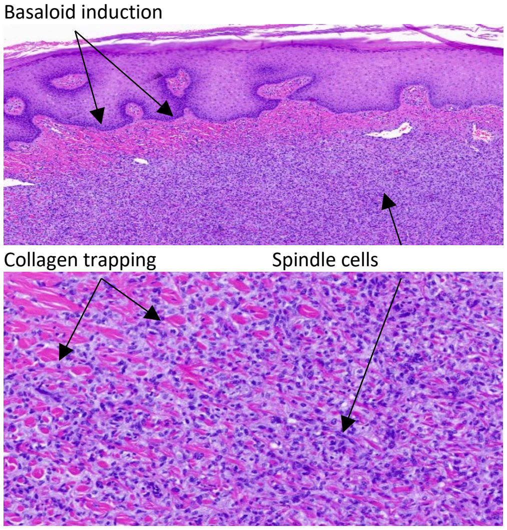
8. BONE AND SOFT TISSUE PATHOLOGY



FIBROUS HISTIOCYTOMA (DERMATOFIBROMA)

MORPHOLOGY

- **Plump cytologically bland**, **ovoid to spindled cells** with **vesicular chromatin** and **delicate nucleoli** and **eosinophilic cytoplasm** with indistinct borders**,** arranged in **storiform or short fascicles**
- **Collagen trapping** at edges
- Overlying epidermis may show **basaloid induction**
- Vessels often have a **"staghorn" appearance**
- Lesion is **well-circumscribed** with **thin pseudocapsule**

OTHER HIGH YIELD POINTS

- **Rare neoplasm**, wide age of presentation, **slight male sex predilection**
- **Painless, slow-growing mass** in the **extremity** subcutaneous tissue
- **Recurrence** after surgery is **frequent**, **metastasis** is very **rare**
- **Variants**: Deep benign, plexiform, aneurysmal, epithelioid, cellular
- **IHC**: **positive for CD34 and Factor XIIIA**; negative STAT6, EMA, desmin

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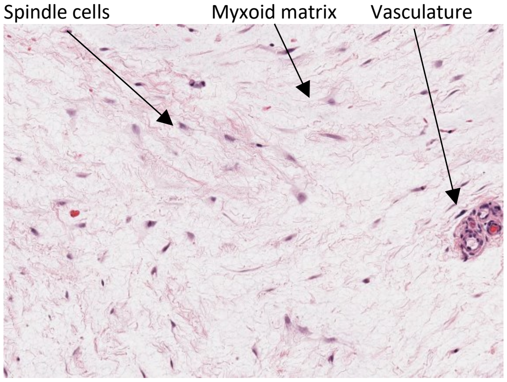
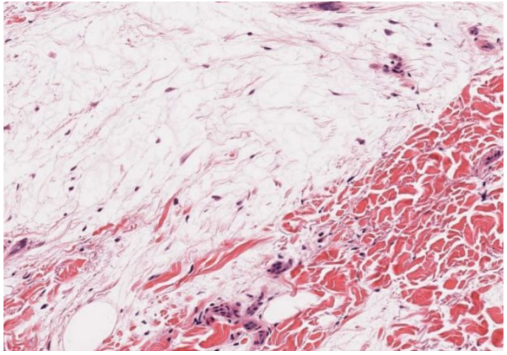
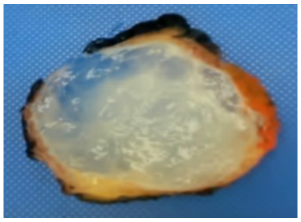
TUMORS OF UNCERTAIN DIFFERENTIATION



Myxoid matrix interspersed through collagen





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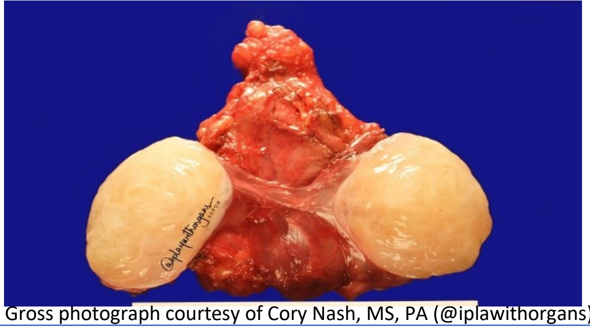
MYXOMA

MORPHOLOGY

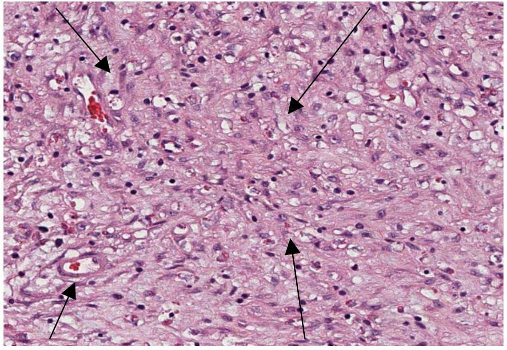
- **Bland**, **uniform spindled** to **stellate cells** with oval nuclei and **fibrillary** or **tapered cytoplasm** suspended in a **myxoid matrix**
- **Sparse vasculature** and spindle cells lack condensation around vessels
- **No necrosis**, **no mitosis**
- Often has cystic change and myxoid matrix can intersperse through collagen

OTHER HIGH YIELD POINTS

- Can arise in various locations in the body
- **Intramuscular:** female predominance, most common in thigh
- **Juxta-articular:** male predominance, majority occur in knee
- **Cardiac:**
  - **Sporadic type** (majority of cases) → females
  - **Familial type** → males
- May be associated with **genetic syndromes** → **Mazabraud syndrome**
  - **Mazabraud: Intramuscular myxoma** and **fibrous dysplasia**
- **IHC: most important → negative for MUC4; variable CD34 and SMA**
- **Molecular**: **Activating mutation of *GNAS* at codon 201**
  - Seen in **sporadic**, **cellular**, **non-cellular**, and **Mazabraud syndrome**
  - **Juxta-articular does not have GNAS mutations**
  - **Familial cardiac myxomas** → heterozygous **PRKAR1A** (17q24) **mutation**
  - **Sporadic cardiac myxomas** → no **GNAS**, no **PRKAR1A** mutations



Gross photograph courtesy of Cory Nash, MS, PA (@iplawithorgans)



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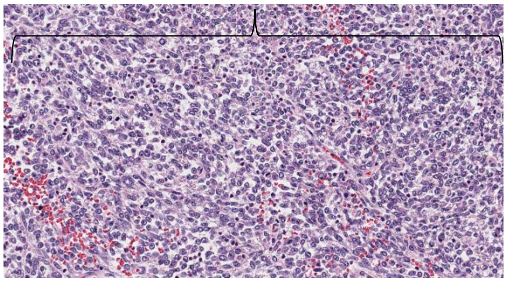
DEEP AGGRESSIVE ANGIOMYXOMA

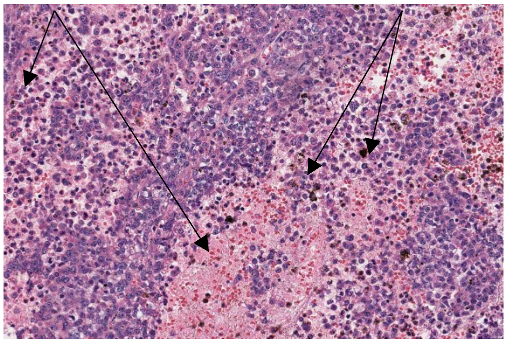
MORPHOLOGY

- **Spindled to stellate cells** with **no significant atypia** that are suspended in **abundant myxoedematous** stroma
- **Vascularity has variation** (thin-wall capillaries → thick-walled vessels)
- **Collagen fibers scattered** throughout **myxedematous stroma**
- Often **low cellularity** and has an **infiltrative growth** pattern
- **Extravasated red cells** and **scattered mast** cells common

OTHER HIGH YIELD POINTS

- **Benign tumors** occurring mainly in **women** in a wide age range
- Clinically presents as a **slow-growing mass** in the **pelvicoperineum**
- Recurrence is seen in ~40% of cases
- **IHC**: positive for ER, PR, and desmin
- **Molecular**: Rearrangements in **HMGA2 (12q13-15)** → t(8;12) or t(11;12)





EXTRARENAL RHABDOID TUMOR

MORPHOLOGY

- **Polygonal rhabdoid cells** with **eccentric vesicular nuclei**, **conspicuous nucleoli**, +/- **intranuclear** inclusions, and **glassy eosinophilic cytoplasm**
- **Rhabdoid cells** are arranged in **trabeculae** or **solid sheets**
- **Necrosis** and **hemosiderin** are seen in the background
- Infiltrative peripheral borders

OTHER HIGH YIELD POINTS

- Rare, **highly malignant neoplasms** seen in **infants** and **young children**
- Mainly in **axial locations** → **neck**, **spine**, **retroperitoneum**, thigh
- **Clinically**: **rapidly enlarging mass** that ulcerates overlying skin
- **Prognosis**: **very poor, ~10% survival** → often recurrence/metastasis
- **Treatment**: Total neoadjuvant then surgical resection
- **IHC**: **Positive CD99** (~50%), **synaptophysin** (~50%), vimentin, keratins (CK8, CK18), and SALL4; **negative for INI1** (non-specific)
- **Molecular**:
  - ➢ **Homozygous deletions** or **monosomy of chromosome 22q11.2** → **SMARCB1/INI1** tumor suppressor gene
  - ➢ Translocations involving 1p, 6p, 11p, or 18q

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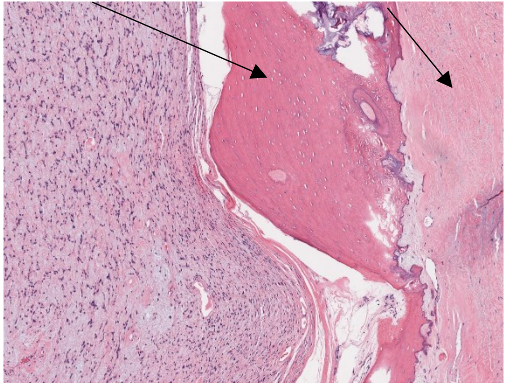


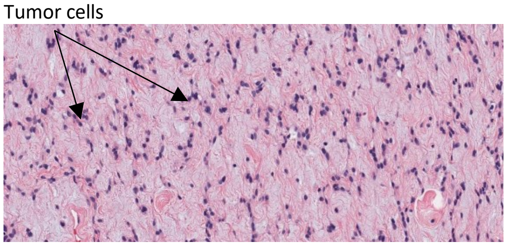
OSSIFYING FIBROMYXOID TUMOR

MORPHOLOGY

- **Uniform** oval to round tumor cells, **bland nuclei** and **pale eosinophilic cytoplasm**; arranged in nodules with **fibrous pseudocapsule**
- **Stroma is variable** → fibromyxoid, myxoid, or hyalinized
- **Ossification present**, no necrosis or vascular invasion

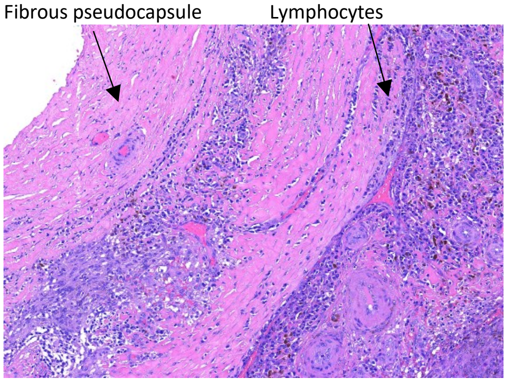
OTHER HIGH YIELD POINTS

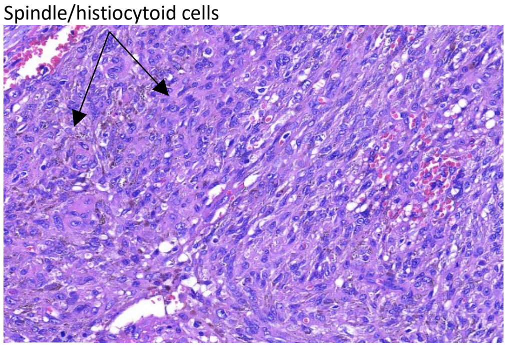
- **Rare tumor** occurring in **middle-aged** with **a 2:1 male predominance**
- Morphologic variants
  - ➢ **Atypical OFMT:** increased mitotic activity (>2/ 50 HPF) or high cellularity and low mitotic rate (<2 mitoses /50HPF)
  - ➢ **Malignant OFMT:** high nuclear grade, >2 mitoses/50HPF, extracellular matrix absence and overlapping nuclei in a single 4x field; typically has necrosis
- **IHC**: **Positive S100**; +/- neuroendocrine markers; loss of nuclear INI1



- Molecular: Rearrangements of *PHF1* (6p21) seen in majority of cases
  - **Most common fusion: EP400-PHF1**
  - **Alternative fusions:** EPC-PHF1, ZCH7B-BOR, CREBBO-BCORL1, KDM2A-WWTR1, or MEAF6-PHF1
  - **PHF1** seen in **benign, atypical,** and **malignant OFMT**

Path Presenter





Path Presenter

ANGIOMATOID FIBROUS HISTIOCYTOMA

MORPHOLOGY

- Spindled to **histiocytoid appearing bland cells** arranged in **short fascicles**, **loose swirls**, or **storiform** pattern
- **Lymphocytic rim "cuffing"** surrounding the entire fibrous pseudocapsule of the lesion. Stroma is variable → fibrosclerotic to myxoid. Variably sized pseudoangiomatous spaces

OTHER HIGH YIELD POINTS

- Rare, **seen in children and young adults**, **slight female predominance**
- **Clinically**: a **painless**, **slow-growing** mass in superficial extremities
- Recurrence rate is variable, metastasis is rare
- **IHC**: **positive for ALK**, desmin; negative for MyoD1, myogenin, CD31, S100
- **Molecular**: Chromosomal translocations
  - **Most common (90%): EWSR1-CREB1 → t(2;22)(q33:q12)**
  - **Extrasomatic cases: EWSR1-ATF1 → t(12;22)(q13:q12)**
  - **Uncommon:** FUS-ATF1 → t(12;16)(q13:q12)

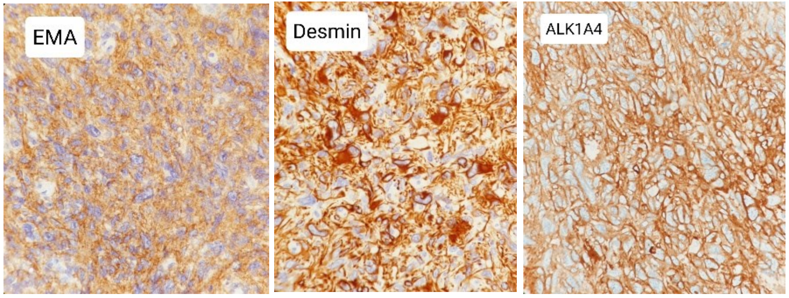
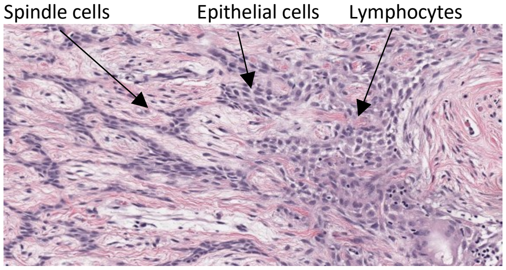


Image Credit: Raul Perret, MD, MSc @kells108



ECTOPIC HAMARTOMATOUS THYMOMA

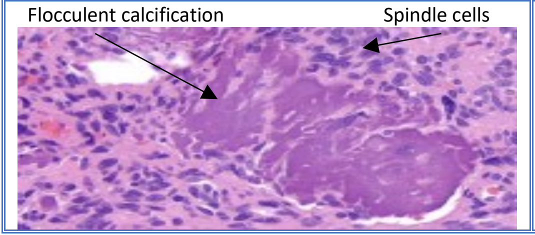
MORPHOLOGY

- **Haphazard proliferation** of **epithelial** cells, **spindle cells**, and **adipocytes**
- Bland spindle cells seen in sheets, storiform, lattice, or short fascicles
- Epithelial cells are **predominantly squamous**
- **Low mitotic activity**; lymphocytic infiltrate present but subtle

OTHER HIGH YIELD POINTS

- **Extremely rare**, seen in **male adults**
- Unrelated to the thymus (despite name)

Path Presenter



PHOSPHATURIC MESENCHYMAL TUMOR

MORPHOLOGY

- **Bland spindled and stellate cells** in a background of **chondromyxoid** or **hyalinized matrix material**, scattered **flocculent calcifications**
- Stromal capillary vasculature; osteoclast-like multinucleated cells

OTHER HIGH YIELD POINTS

- **Very rare**, **middle-aged adults** with pain/stress fractures in thigh, foot

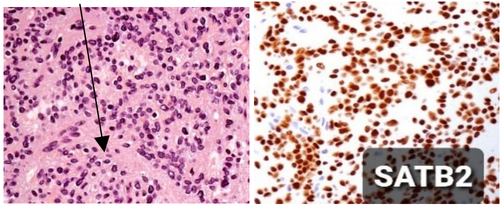
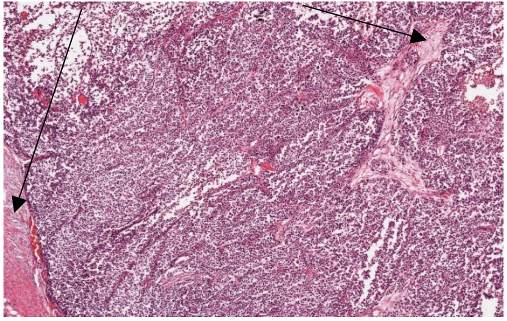
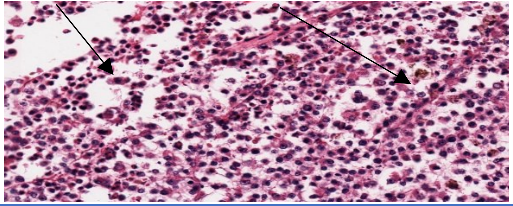


Image Credit: Raul Perret, MD, MSc @kells108

- **Mechanism of development**:
  - **Produces FGF23 → inhibits** proximal renal tubule **re-uptake of phosphorus → osteomalacia**
- **Laboratory** abnormalities **common → hypophosphatemia** and **hyperphosphaturia** but **calcium is normal**
- **IHC**: Positive for **FGF23**, **SATB2**,**ERG**, and CD56; negative for STAT6, DOG-1, and CD34
- Molecular: **FN1-FGFR1 fusion** seen in ~50% of cases





CLEAR CELL SARCOMA OF SOFT TISSUE

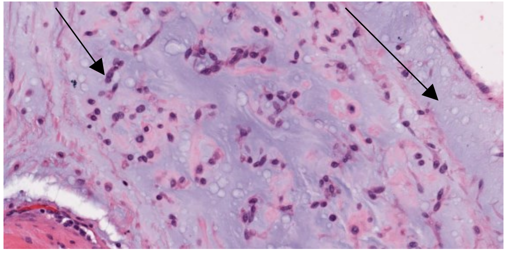
MORPHOLOGY

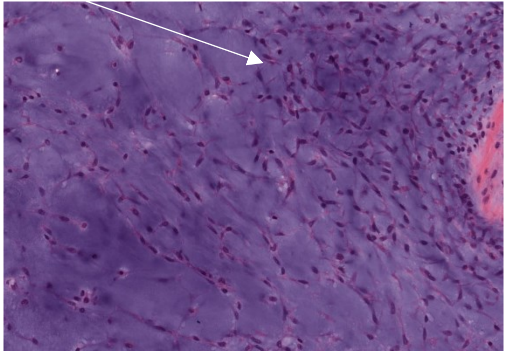
- **Monotonous ovoid to spindle cells** with nuclei that have **conspicuous nucleoli**, and **clear cytoplasm** and arranged in **fascicles** and **nests**
- Cells may also have **melanin pigment** (often focal)
- **Collagen separates nests** and is either sclerotic/dense or delicate
- Scattered **multinucleated giant cells** with **peripherally located nuclei** characteristic → "**wreath cells**"

OTHER HIGH YIELD POINTS

- **Rare malignancy** seen in predominantly **white young adults**
- Clinically: **mass arising in the extremities** → **feet** most common
- **Prognosis is poor**,20-year survival is <10%
- **Important prognostic factors**: recurrence, size (>5 cm), necrosis
- Often has **late metastasis** or recurrence up to **20 years later**
- **IHC**: **positive** for **all melanocytic markers**
- **Molecular**: Most have translocations
  - **Most common: EWSR1-ATF1 → t(12;22)**
  - Uncommon: EWSR1-CREB1 → t(2;22)

Path Presenter





Path Presenter

EXTRASKELETAL MYXOID CHONDROSARCOMA

MORPHOLOGY

- **Monotonous proliferation** of round to **spindle-shaped cells** with minimal **eosinophilic cytoplasm**; arranged in **cords**, **clusters**, and **nests** with a "hand holding" type of look
- Background has **abundant chondromyxoid matrix**
- **Necrosis**, **hemorrhage**, and hemosiderin are common

OTHER HIGH YIELD POINTS

- **Rare sarcoma**, seen in **middle-aged men** as a **lower extremity mass** with larger tumors decreasing range of motion
- **Most common site** of **metastasis** is the lungs
- **IHC**: Positive for S100 and EMA but non-specific
- **Molecular**: Various fusions with NR4A3 are reported
  - **Most common:** EWSR1-NR4A3 → t(9;22)(q22;q12.2)
  - Others: t(9;17)(q22;q11.2)

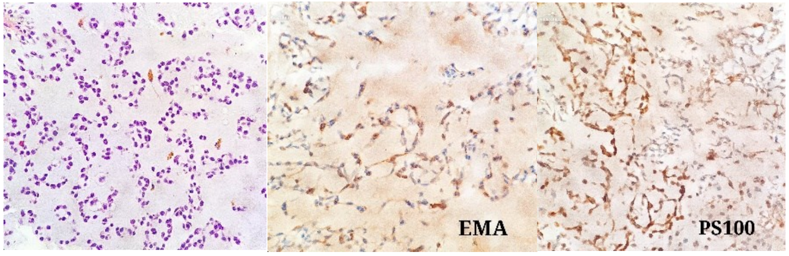
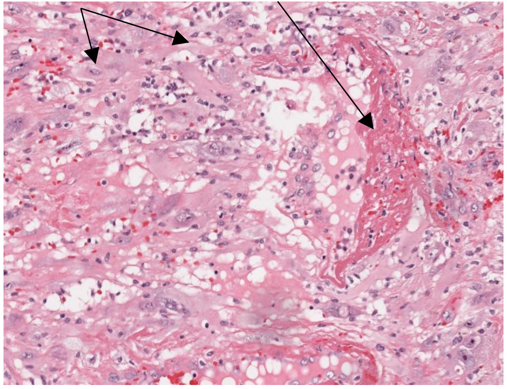
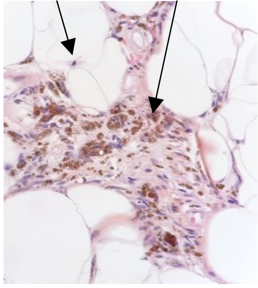


Image Credit: Raul Perret, MD, MSc @kells108





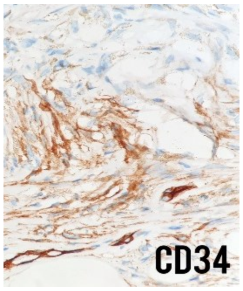


Image Credit: Raul Perret, MD, MSc @kells108

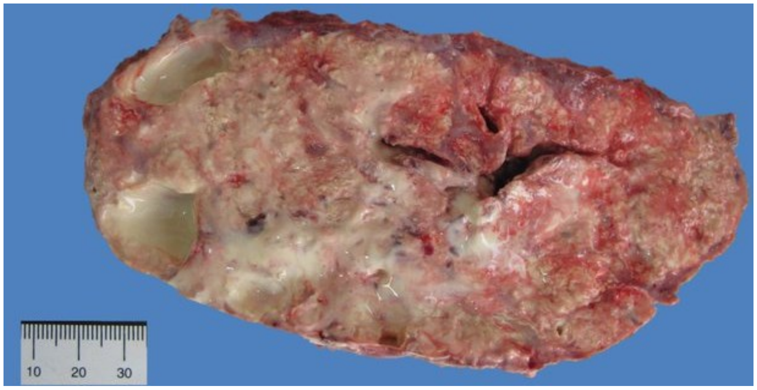
PLEOMORPHIC HYALINIZING ANGIECTATIC TUMOR/HEMOSIDEROTIC FIBROLIPOMATOUS TUMOR

MORPHOLOGY

- **Spindle cells** with **nuclear hyperchromasia** and **conspicuous nuclear pleomorphism** adjacent to **variably sized blood vessels** lined by **fibrin**
- Adipocytes with admixed hemosiderin-laden spindle cells

OTHER HIGH YIELD POINTS

- Rare, **middle-aged slight female predominance**; **foot/ankle mass**
- High local **recurrence rate** (up to 50%), no metastasis
- **Molecular**: **TGFBR3** or **MGEA5** rearrangements, CD34+/-



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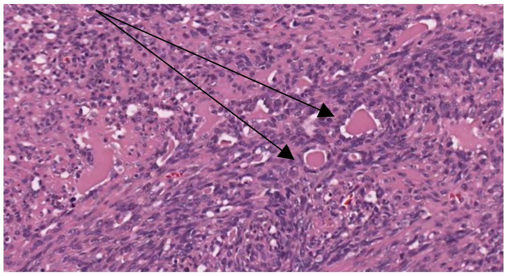
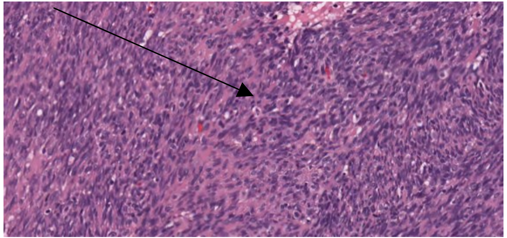
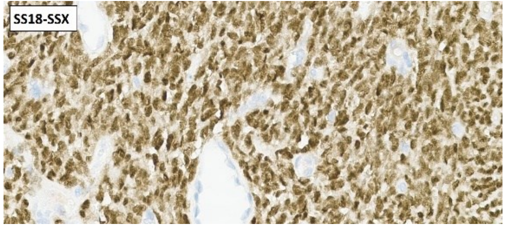






Courtesy of Raul Perret, MD, MSc @kells108

SYNOVIAL SARCOMA

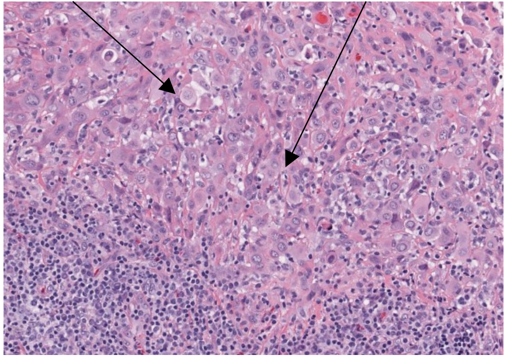
MORPHOLOGY

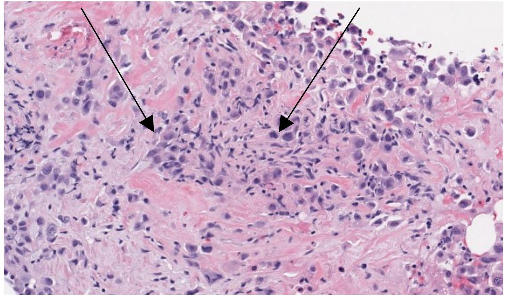
- **Spindle cells** with **ovoid nuclei** and **minimal cytoplasm** arranged in **cellular sheets** or **fascicles**
- **Variable collagenous stroma** and may be **wiry** and **have calcifications**
- Can have an **epithelioid component** with round to ovoid nuclei, conspicuous nucleoli, and eosinophilic cytoplasm arranged in nests or glandular structures
- Prominent vessels seen and are "**staghorn**" in appearance

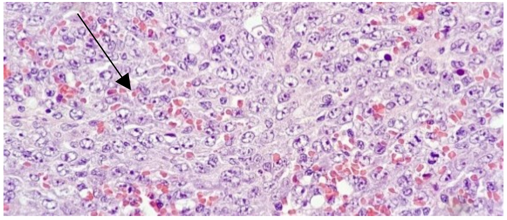
OTHER HIGH YIELD POINTS

- Typically seen in **young adults <50 years** old
- Most arise in **extremities near joints** → particularly the **knee**
- Deep situated, slow-growing mass and 50% are painless
- Histologic variants:
  - **Monophasic:** spindle component only
  - **Biphasic:** spindle and epithelioid component
- **Metastasis** in about 50% of cases
- **Unfavorable prognostic** factors:
  - **Large** tumor **size**
  - **Age >40**
  - **Poorly differentiated** in 20% or more of tumor
  - **High-stage** at diagnosis
- **IHC**: Positive for **SSX**, **SS18**, **TLE1**, CD56, CD99, keratin, EMA; negative for NKX2.2, PAX3, CD34, myogenin
- **Molecular**: Characteristic translocation
  - **Most common: SSX1-SS18 fusion → t(x;18)(p11;q11)**

Path Presenter







EPITHELIOID SARCOMA

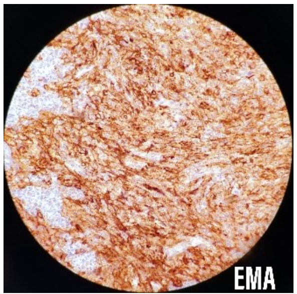
MORPHOLOGY

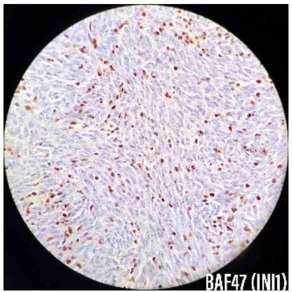
- **Classic type:** Cellular nodules of epithelioid to spindled cells with vesicular nuclei, **conspicuous nucleoli**, and **eosinophilic cytoplasm**; can look granulomatous
- Often have central degeneration and necrosis
- **Proximal type:** sheet-like growth of large pleomorphic rhabdoid-appearing cells with similar nuclear features to spindled cells
- Mitosis is very common

OTHER HIGH YIELD POINTS

- Rare, aggressive sarcoma, seen in young adult males or older males
- Two main types:
  - **Conventional/Classic** → seen in **young** adult **males**
  - **Proximal** → seen in **middle-aged** or **older male** adults
- **Majority** of cases recur, and half metastasize to lymph nodes and lungs
- Proximal type has a worse prognosis →5-year survival is 30%
- Adverse prognostic factors:
  - **Location** (proximal or deep sites), **male sex**, and size **>5cm**
- **IHC: Loss of INI1;** positive for EMA, keratins, CD34, ERG, GLUT1; negative for FLI-1 and PROX1
- **Molecular**: Deletion of 22q11 → SMARCB1 (INI1)

Path Presenter





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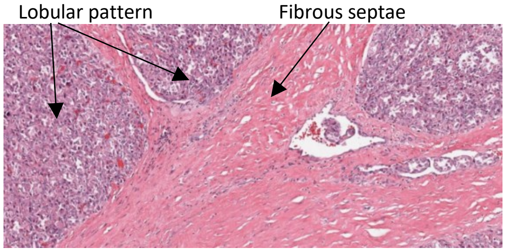
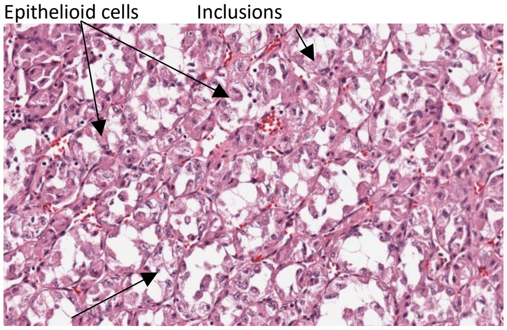




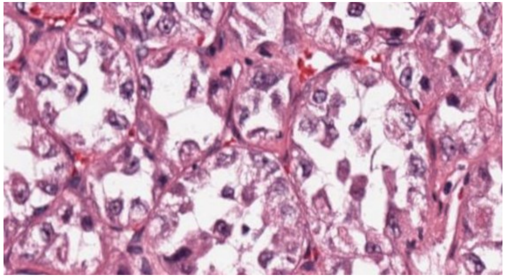
ALVEOLAR SOFT PART SARCOMA

MORPHOLOGY

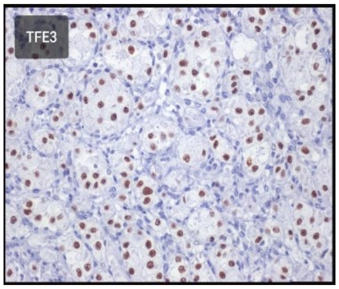
- Large, **uniform epithelioid cells** with **round nuclei** and **conspicuous nucleoli**, and **abundant** granular **eosinophilic cytoplasm**
- **Compartmentalization** → **lobules**, nests with **fibrocollagenous septa**
- Rod to rhomboid-shaped intracytoplasmic inclusions
- **Pseudoalveolar pattern** → **tumoral nests** with an **empty central portion** due to **absence of cohesion** and degeneration
- **Necrosis** is **uncommon** and mitotic activity is low

OTHER HIGH YIELD POINTS

- **Rare** and predominantly seen in **infants** and **young adults** with a **female predominance**; **slow-growing mass** in **anterior thigh/buttocks**
- **Metastasis present in 50%** of patients at diagnosis
- **Poor prognosis** → present with metastasis to lung and brain
- Most important **favorable factors**:
  - **Small size (<5 cm), young age** at diagnosis **(<10), no metastasis**
- **IHC**: **Positive** for **TFE3**; variable S100 and desmin
- **Special stains**: **PAS** highlights intracytoplasmic inclusions
- **Molecular**: **der(17)t(X;17)(p11.2;q25)** → ASPSCR1 (ASPL)-TFE3 fusion


Irregular nuclei
Discohesive

Path Presenter



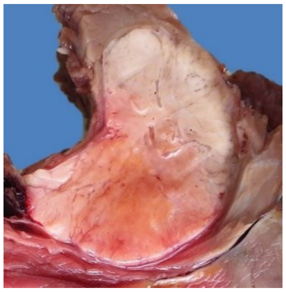
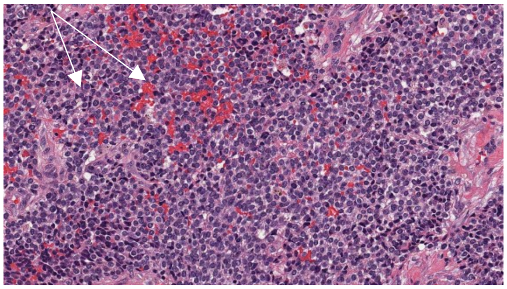
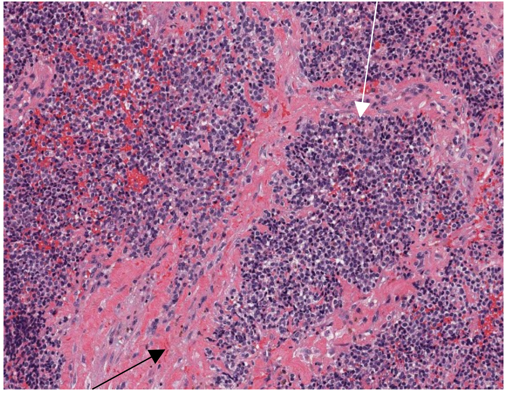
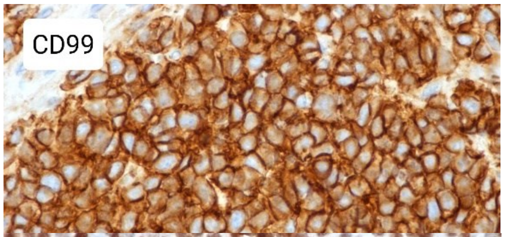
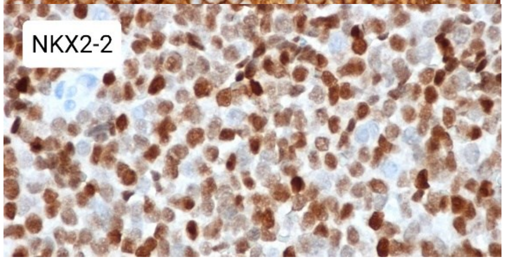


Image Credit: Raul Perret, MD, MSc @kells108


Round cells


Lobular pattern
Variable fibrosis





IHC images courtesy: Raul Perret, MD, MSc @kells108

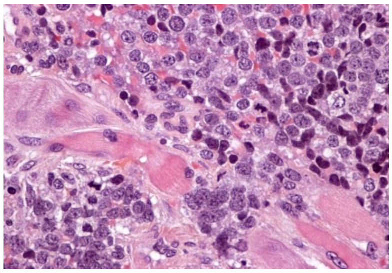
EWING SARCOMA

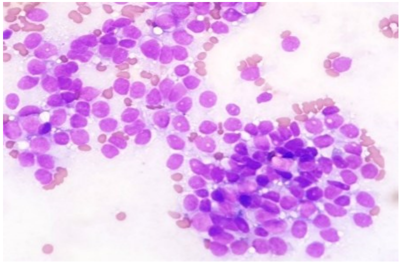
MORPHOLOGY

- **Uniform round blue** cells with **finely granular chromatin** and **occasional nucleoli**, and **vacuolated cytoplasm**
- **Sheet-like or lobular growth** pattern; **rosettes** may be seen
- **Inconspicuous mitosis**
- **Necrosis** and **apoptosis** are typical and scattered about

OTHER HIGH YIELD POINTS

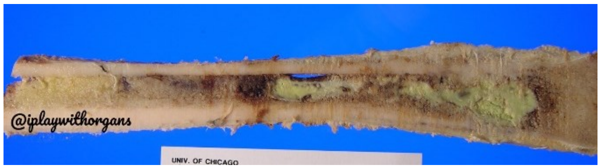
- **Young adults**, **painful mass**, **fever**, **weight loss**, **pathologic fracture**
- **Most** common **affected** bones are the **femur**, **tibia**, and **humerus**
- **Radiographic**: "**moth-eaten**" appearance of bone
- **Metastasis** occurs early → typically to the lungs
- **Favorable prognosis**: **age (<10)**, **location** (non-pelvic bone), <8 cm size
- **IHC**: **positive** for **CD99**, **vimentin**, and **FLI**1
- Molecular: Several translocations
  - **Most common (95%):** EWSR1-FLI1 → t(11;22)(q24;q12)
  - Type 1 fusion **better prognosis:** EWSR1 exons 1-7 fuse to FLI1 exons 6-9
  - **Less common:** EWSR1-ERG → t(21;22)(q22;q12)
  - Alternatives, less than 5% of cases:
    - EWSR1-E1AF → t(17;22)(q12;q12)
    - EWSR1-PATZ1 → t(1;22)(p36;q12)
    - EWSR1-ETV1 → t(7;22)(p22;q12)
    - EWSR1-FEV → t(2;22)(q33;q12)


Muscle infiltration

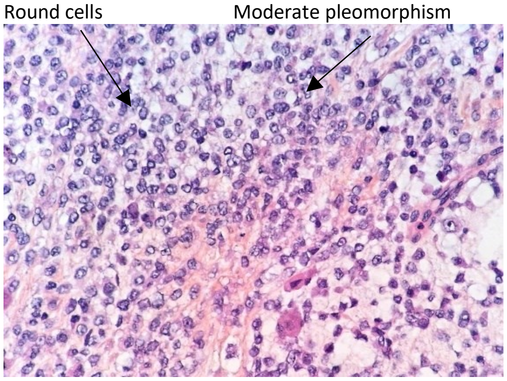

"Round blue cells" on Cytologic Prep

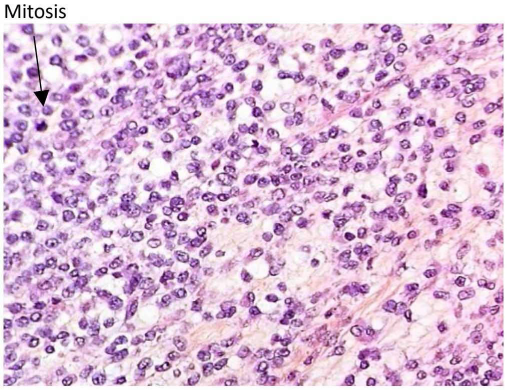
Images courtesy: Raul Perret, MD, MSc @kells108

Path Presenter


@iplaywithorgans
UNIV. OF CHICAGO

Courtesy of: Cory Nash, MS, PA (@iplaywithorgans)





UNDIFFERENTIATED ROUND CELL SARCOMA WITH CIC-DUX4 TRANSLOCATION

MORPHOLOGY

- **Proliferation of small round** cells with **moderate nuclear pleomorphism**, **coarse chromatin**, **conspicuous nucleoli**, and indistinct cytoplasm
- Lobular architecture and has **geographic necrosis**
- Most have a **myxoid matrix**, and **numerous mitoses** are seen

OTHER HIGH YIELD POINTS

- **Very rare**; **seen in children** and **young adults**; **extremity** or **trunk mass**
- Majority have metastasis at diagnosis → lung; most dead at 2 years
- IHC: **positive** for **WT1**, **ETV4, CD99**
- **Molecular**:
  - ➢ **CIC-DUX4 translocation → t(4;19)(q35;q13.1)**
  - ➢ **Alternative**: t(10;19)(q26.3;q13)
  - ➢ **Trisomy 8 frequently** seen
  - ➢ **Post treatment → complex karyotype**

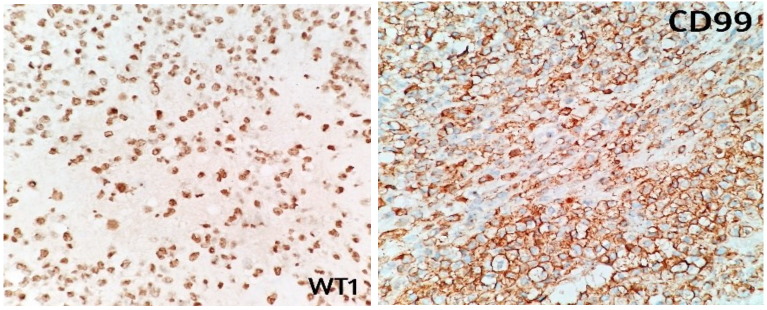
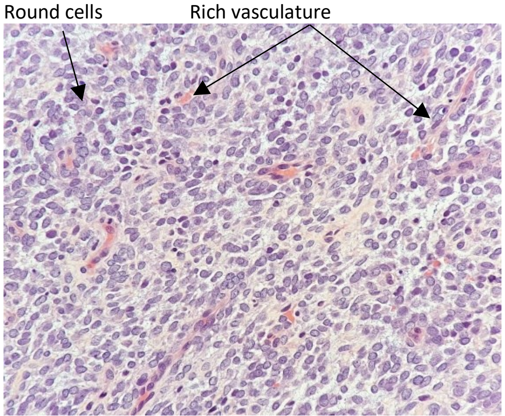
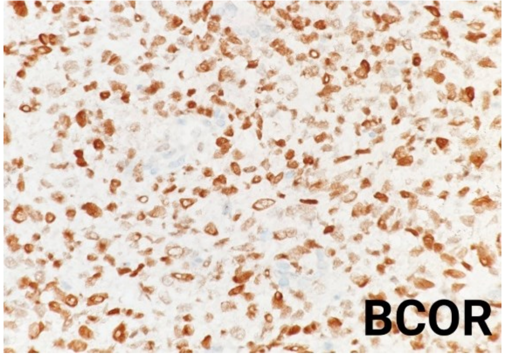


Image Credit: Raul Perret, MD, MSc @kells108





Images courtesy: Raul Perret, MD, MSc @kells108

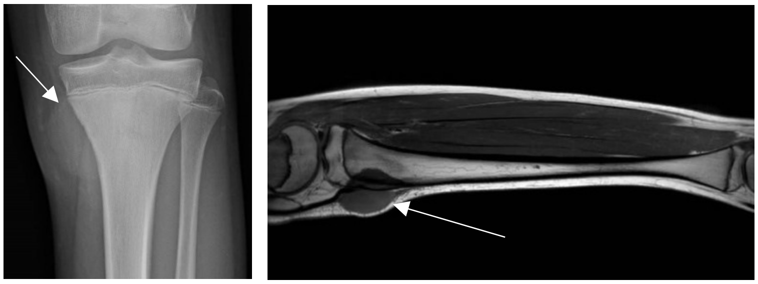
BCOR-CCNB3 Fusion-Positive Sarcoma

MORPHOLOGY

- **Small round** to **plump spindled cells** with **monomorphic round nuclei**, **fine chromatin** and **scant** eosinophilic **cytoplasm**
- **Solid arrangement** of tumor cells with rich vascular stroma
- **Necrosis** is **variable**

OTHER HIGH YIELD POINTS

- **Very rare**, mostly **adolescents** & **young adults**, majority **males**
- Clinically presents as **swelling** and **pain** in the affected bone
- **Uncommon to have metastasis** at the time of diagnosis
- **Survival is better than CIC-rearranged** and similar to Ewing sarcoma
- **5-year survival ~75%** and similar disease-free survival
- **IHC**: **positive** for **BCOR**, CCNB3, CD99, SATB2, TLE1; variable NKX2.2, PAX-8; negative for WT1, ETV4
- **Molecular**: **Inversion of X chromosome** → **BCOR-CCNB3** fusion
  - ➢ **Less common:** BCOR-MAML3; BCOR internal tandem duplication



Images courtesy: Raul Perret, MD, MSc @kells108

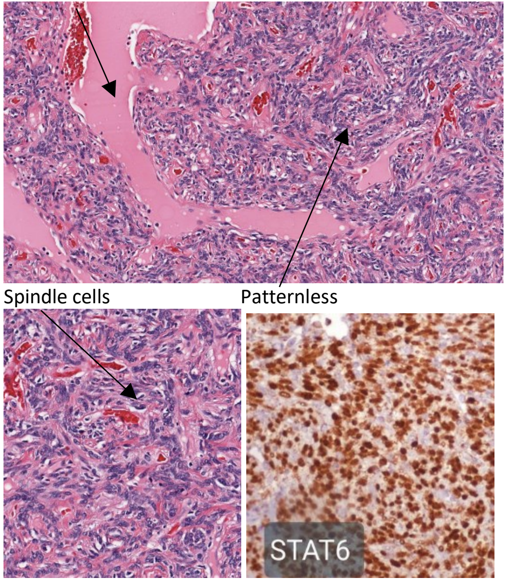


Image Credit: Raul Perret, MD, MSc @kells108

SOLITARY FIBROUS TUMOR

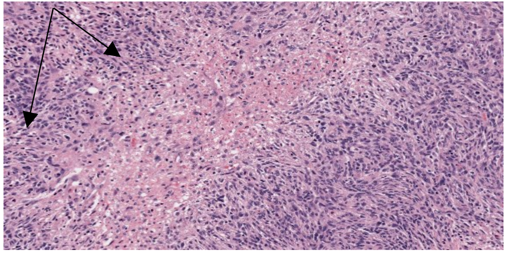
MORPHOLOGY

- Ovoid to spindled fibroblastic cells with vesicular nuclei and scant cytoplasm
- Tumor cells are in a "patternless" pattern
- Cellularity is variable
- Prominent vessels with thin walls and branching → "Staghorn" appearance
- Mast cells commonly present

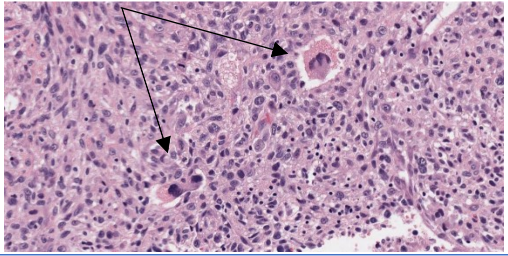
OTHER HIGH YIELD POINTS

- Usually seen in adults with no sex predilection with few exceptions
  - **Lipomatous variant**: slight **male** predominance
  - **Superficial variant**: strong **female** predominance
- Often occurs **thoracic cavity**, **extremities**, viscera, head and neck
- **Risk stratification** based on tumor size, age, mitotic activity, and necrosis
  - **Atypical features:** >4 mitoses /10HPF, cellular, pleomorphism, necrosis, infiltrative margins
  - **Malignant features:** abrupt transition to high-grade sarcoma, heterologous elements
  - **Heterologous elements:** rhabdomyosarcomatous or osteosarcomatous
- **IHC**: **Positive** for **STAT6**, CD34
- **Molecular**: **NAB2-STAT6** gene fusion

Path Presenter



Severe pleomorphism



INTIMAL SARCOMA

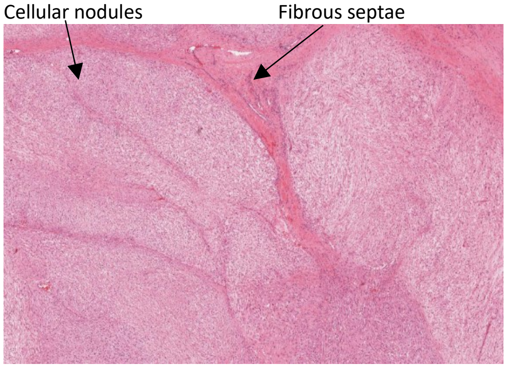
MORPHOLOGY

- **Poorly differentiated spindle cells**, **moderate** to **severe pleomorphism**
- Tumor cells **arising in the wall** of **large** blood **vessels**
- Often has **seeding tumor emboli**
- May have **myxoid** (common) or fascicular patterned areas

OTHER HIGH YIELD POINTS

- **Rare** and **occurs** in **older adults**
- Usually in the **pulmonary trunk** or **artery** with **direct extension into** the **pulmonary valve** and **right ventricle**
- Has **distant metastasis**: liver, peritoneum, bone, and mesenteric lymph nodes
- Most common to be **discovered at autopsy**
- **Mortality is >80%** at one year
- **IHC**: positive for **MDM2** (nuclear); **negative** for **endothelial markers**
- **Molecular**: Chromosomal gains or amplifications (MDM2, EGFR, PDGFRA)

Path Presenter



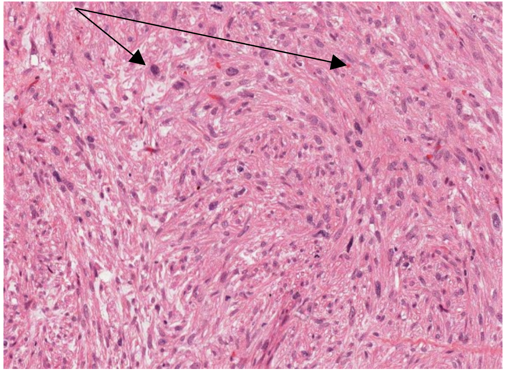
UNDIFFERENTIATED SARCOMAS

MORPHOLOGY

- **Highly cellular tumor** composed of **atypical spindled** or **polygonal cells** with **marked nuclear pleomorphism**, **multinucleation** or **bizarre nuclei**, and amphophilic to **eosinophilic cytoplasm**
- **Variable stroma**, most often **collagenous** or focally myxoid & sclerotic
- **Abundant mitosis** (and atypical) and **necrosis**

OTHER HIGH YIELD POINTS

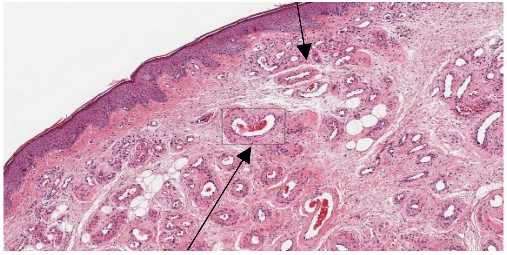
- Most common in **older to elderly males** (Males >> females)
- **Subfascial mass** of **lower extremity** → most common is **thigh**
- May be associated with the **history of radiation** to the area
- **Morphologic variants** are **named** based **on morphology**
  - Undifferentiated spindle cell sarcoma

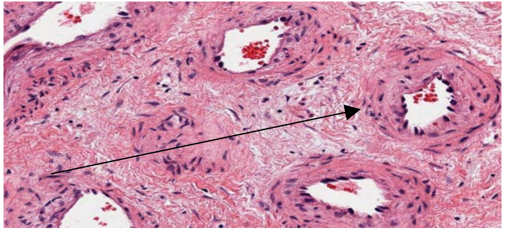


  - Undifferentiated round cell sarcoma
  - Undifferentiated epithelioid sarcoma
  - Undifferentiated pleomorphic sarcoma (Malignant fibrous histiocytoma)
- **Local recurrence** is seen **in ~30-40%**
- **Distant metastasis**:~50% of cases → **most common** is **lung**
- **Poor outcome**, survival at 5 years is ~50%,
- **IHC**: Negative for keratins, CD31, CD34, S100, CD163, CD68, CD45, CD30, SMA, desmin, myogenin, MyoD1, ERG, p63
- **Molecular**: nonspecific complex karyotypes

Path Presenter

VASCULAR LESIONS





VASCULAR MALFORMATIONS

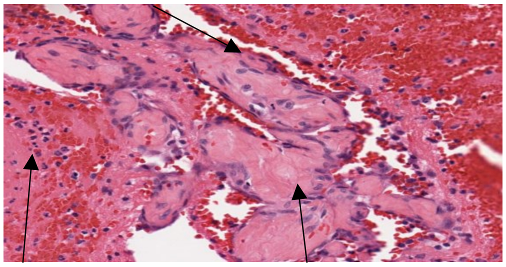
MORPHOLOGY

- Large **tortuous arteries** with **fragmented elastic lamina**, associated with **thick-walled veins** and variable small vessel component

OTHER HIGH YIELD POINTS

- **Venous malformations** (venous hemangiomas) are poorly circumscribed collection of abnormal veins
  - Vary in size/proportion
  - Often abnormally thick or thin walls
  - Includes cavernous hemangiomas (collection of large, dilated veins with thin walls)
- **Cutaneous capillovenous malformation**
  - Often diagnosed clinically (e.g. Telangiectasia)
  - Associated with a variety of conditions (e.g. Osler-Weber-Rendu)
- **Intramuscular hemangioma** shows small vessels (often parallel) in muscle

Path Presenter



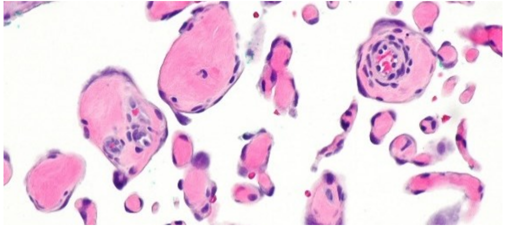


Image courtesy of Dr. Michael Bonert

PAPILLARY ENDOTHELIAL HYPERPLASIA (*aka Masson Tumor*)

MORPHOLOGY

- **Intravascular** exuberant **proliferation** of **endothelial cells** with **fibrin**
- **Small papillae** covered by a single layer of endothelium with a **collagenized fibrin core**
- Papillae can fuse, forming **anastomotic channels**
- **No atypia or mitoses**

OTHER HIGH YIELD POINTS

- **Can mimic angiosarcoma** and can be distinguished by exclusively intravascular growth and **lack of mitosis/atypia**

Path Presenter

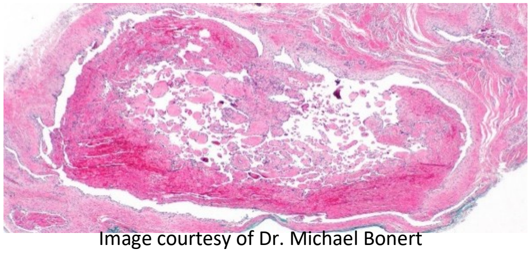
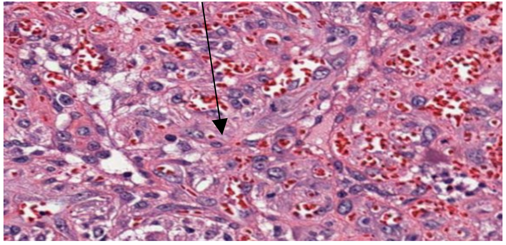
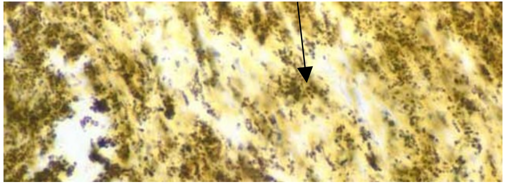


Image courtesy of Dr. Michael Bonert

8. BONE AND SOFT TISSUE PATHOLOGY


Plump endothelial cells


Warthin-Starry stain

Organism

Provided by: Kauczuk on Wikimedia

BACILLARY ANGIOMATOSIS

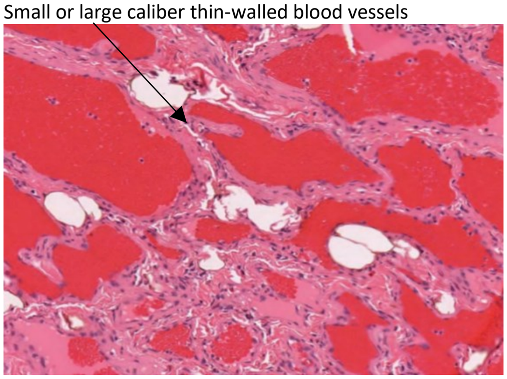
MORPHOLOGY

- Lobules of capillary-sized vessels with plump endothelium with clear to eosinophilic cytoplasm
- Associated with **neutrophilic infiltrate**

OTHER HIGH YIELD POINTS

- Pseudo-neoplastic vascular proliferation caused by **Bartonella**
- Can be **Bartonella Henselae** or **Bartonella Quintana**
  - Gram-negative **intracellular** bacilli
  - Can see concomitant Cat-Scratch Disease
  - **B. Henselae** transmitted by **cat**
  - **B. Quintana** transmitted by **flea or louse bites**
- **Special stains: Warthin-starry** stain highlights the organisms, but can be difficult to read due to stain precipitation
- Treatment includes antibiotics

Path Presenter


Small or large caliber thin-walled blood vessels

HEMANGIOMA

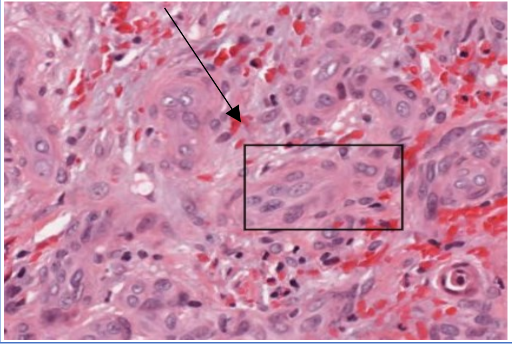
MORPHOLOGY

- Tumor composed of **small or large caliber thin-walled** blood **vessels**
- Single layer of non-atypical endothelial cells

OTHER HIGH YIELD POINTS

- **Benign neoplasm**
- Categorized by vessels size/appearance
  - **Lobular Capillary Hemangioma** ("Pyogenic granuloma")
  - **Infantile (Juvenile) Hemangioma**
  - **Rarer subtypes:** Hobnail hemangioma, Anastomosing hemangioma, Spindle cell hemangioma

Path Presenter


Large epithelioid cells with dense eosinophilic cytoplasm

EPITHELIOID HEMANGIOMA

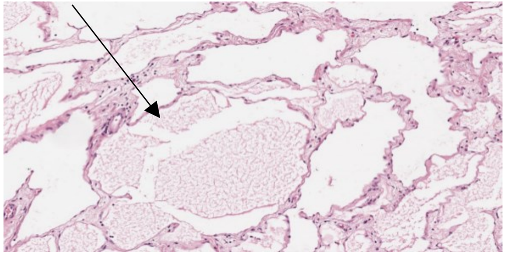
MORPHOLOGY

- Large **epithelioid endothelial cells** with densely eosinophilic cytoplasm, distinct **vasoformation**, **lobular architecture** and can have solid areas
- Mitoses are infrequent and not atypical
- Often rich inflammatory infiltrate comprising of **eosinophils**

OTHER HIGH YIELD POINTS

- **Benign** neoplasm seen in wide age range
- Presents as a **slow-growing** dermal nodule
- IHC: **Positive for vascular markers** (ERG), keratins, EMA; **negative** for **HHV8**
- Molecular: **Rearrangements of FOS** or **FOSB** (seen in **atypical** cases)

Path Presenter


Dilated lymphatics with fluid

LYMPHANGIOMA

MORPHOLOGY

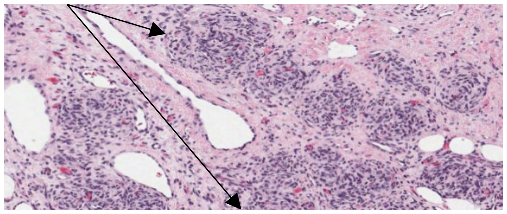
- Thin-walled, variable **dilated** lymphatics, lined by **flattened endothelium**
- Frequently surrounded by lymphoid aggregates
- Contain grossly "milky" lymphatic fluid

OTHER HIGH YIELD POINTS

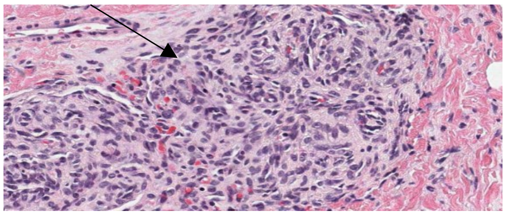
- Associated with **Turner syndrome (XO)**
- Endothelium expresses **D2-40**, **PROX1** (specific for lymphatics) and **CD31**

Path Presenter

Cannon-ball infiltration



Glomeruloid-like structures



KAPOSIFORM HEMANGIOENDOTHELIOMA

MORPHOLOGY

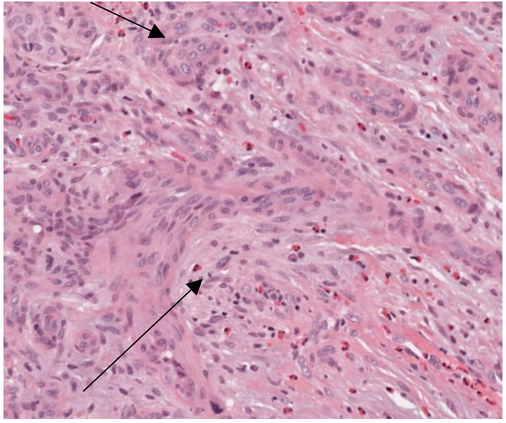
- Infiltrate the soft tissue in **"cannon-ball fashion"**
- Different areas have features of both capillary hemangioma and Kaposi sarcoma (spindle cells)
- Tightly coiled **glomeruloid-like** structures which **may have thrombi**
- **Minimal atypia** is seen in the lesion

OTHER HIGH YIELD POINTS

- Locally aggressive vascular tumor seen in children (50% of cases in 1st year)
  - ➢ Nearly 50% occur within first year of life
- Presents as a **painful mass** or **violaceous plaques**
- Often associated with **Kasabach-Merritt phenomenon**
  - ➢ Consumptive **coagulopathy & thrombocytopenia**
- IHC: **Positive for ERG**, CD34, CD31, PROX1, D2-40; **Negative** for **HHV8**, **GLUT1**

Path Presenter

Epithelioid endothelial cells



Myxohyaline stroma

EPITHELIOID HEMANGIOENDOTHELIOMA

MORPHOLOGY

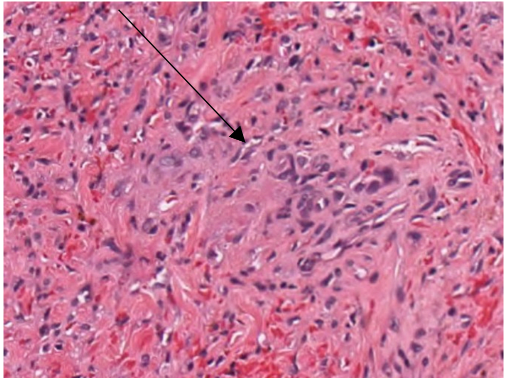
- Cords and nests of epithelioid endothelial cells within **myxohyaline stroma**
- Larger cells with **abundant eosinophilic cytoplasm**, some have **intracytoplasmic lumina with RBCs** ("Blister cells")

OTHER HIGH YIELD POINTS

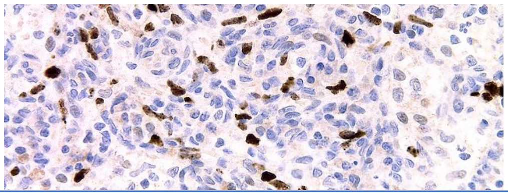
- Malignant (but less aggressive than angiosarcoma), common in liver
- In soft tissue, often angiocentric, expands wall and obliterates lumen
- **High-risk features:** >3cm or >3 mitoses per 50 hpf
- IHC: **Positive** for vascular markers, keratins, EMA, **CAMTA1, TFE3 (minority)**
- **Molecular:**
  - ➢ **WWTR1-CAMTA1** fusion → **t(1;3)(q36;q25)** (majority of cases)
  - ➢ **YAP1-TFE3 fusion** (minority of cases)

Path Presenter

Vasoformative anastomosing channels



IHC: HHV8



KAPOSI SARCOMA

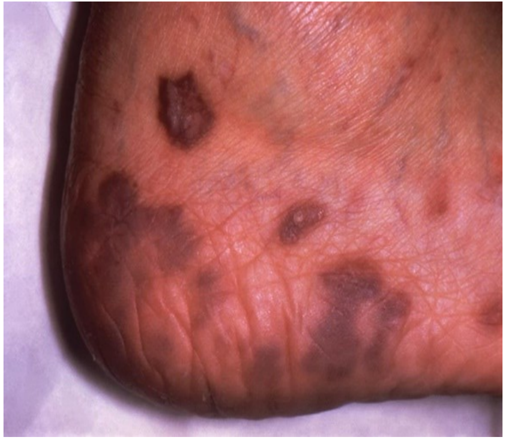
MORPHOLOGY

- Proliferation of bland spindle cells with slit-like vascular spaces containing erythrocytes
- Often associated with inflammatory infiltrate and hyaline globules
- **Patch stage:** Infiltrative vascular channels that dissect collagen fibers
- **Plaque stage:** Spindle cells infiltrate and destroy eccrine glands
- **Tumor stage:** Nodules of intersecting fascicles with "sieve-like" spaces

OTHER HIGH YIELD POINTS

- Locally aggressive, often multiple cutaneous lesions
- **Classic/endemic associated:**
  - ➢ **NOT associated with HIV,** and is **indolent**
  - ➢ Seen in equatorial Africa in children and adults
  - ➢ Association with **podoconiosis** (foot lymphedema from soil exposure)
- **AIDS Associated:**
  - ➢ **Most aggressive** and **presents** at **patch stage**
  - ➢ Usually is seen on the face, genitals, or extremities
  - ➢ **Co-infection** with **HIV1** and **HHV8**
  - ➢ May **regress** or **flare** with HAART

Provided by: Amylacea on Wikimedia

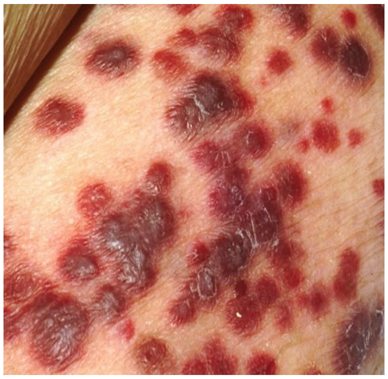


Heel with KS (Endemic): Provided by CDC on Wikimedia

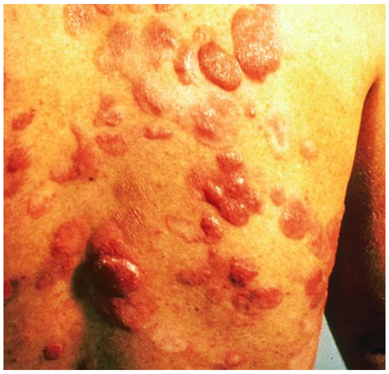
Path Presenter

- **Iatrogenic:**
  - Immunosuppressed individuals and has variable behavior
- **Viral etiology:** caused by Human Herpes Virus 8 (HHV8)
- IHC: Positive for **HHV8 (LANA1)**, ERG, CD31, CD34, D2-40, FLI1

Patch/Plaque Stage of Kaposi Sarcoma

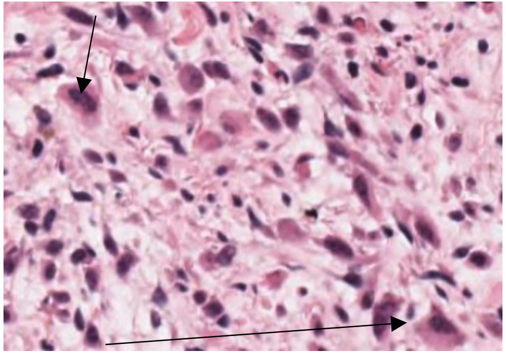


Tumor stage of Kaposi Sarcoma



Photographs courtesy of the NIH on WIkimedia

Plump spindle cells with eosinophilic cytoplasm



Rhabdomyoblast-like cells

PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA

MORPHOLOGY

- **Infiltrative sheets** and **fascicles** of plump **spindle cells** with vesicular nuclei
- Abundant **brightly eosinophilic cytoplasm** (rhabdomyoblast-like)
- Mitoses and intralesional hemorrhage are not readily seen
- May have a brisk infiltrate of neutrophils

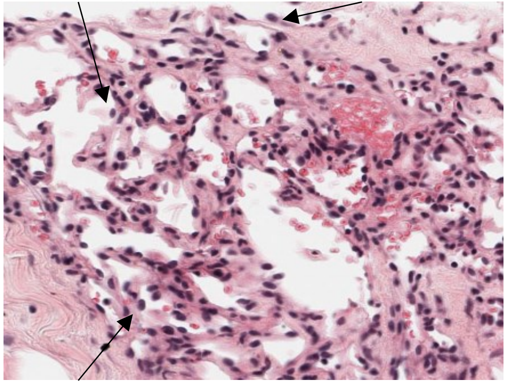
OTHER HIGH YIELD POINTS

- Most common in young adults and has a male predilection
- Mostly arise in the lower extremities
- **IHC**: **Positive** for **CKAE1/AE3**, **ERG**, **FOSB**, **INI1** (intact), variable CD31
- **Molecular**: **SERPINE1-FOSB fusion** → t(7;19)(q22;q13)

Path Presenter

Anastomosing growth

Hobnail



Lacks true cytologic atypia

ATYPICAL VASCULAR LESION

MORPHOLOGY

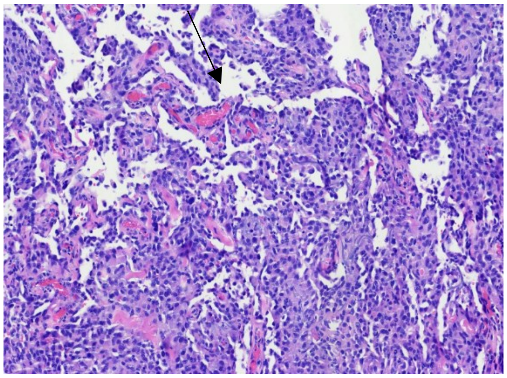
- **Irregularly shaped thin-walled vessels** with branching and anastomosing growth pattern
- Lined by a **single layer** of **endothelial cells** with may be **hyperchromatic** or demonstrate **hobnailing**
- **No true cytologic atypia or endothelial cell multilayering**

OTHER HIGH YIELD POINTS

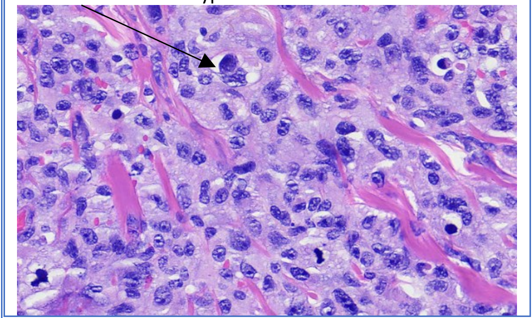
- Benign, often small or multiple and typically seen in middle-aged individuals
- Frequently seen in **irradiated skin** (often breast) and may precedes radiation-induced angiosarcoma (occurs ~10 years later)
- **No MYC overexpression or MYC amplification**

Path Presenter

Vasoformative architecture



Prominent nuclear atypia



ANGIOSARCOMA

MORPHOLOGY

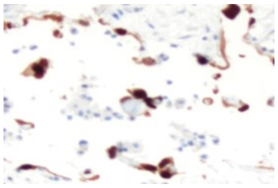
- Endothelial differentiation and can be epithelioid or spindled
- **Vasoformative architecture** and/or expression of endothelial markers
- Often epithelioid in bone with frequent solid growth
- Numerous **extravasated RBCs** and **variable inflammation**, and **necrosis**
- **Prominent nuclear atypia** and **readily observed mitoses**

OTHER HIGH YIELD POINTS

- **High-grade malignancy** which is seen typically in **elderly**
- Presents as a **red-purple** "**bruises**", **plaques**, or **nodules**
- **Post-radiation angiosarcoma** of the **breast**, occurs **~5 years post-radiation**
    - ➢ Can occur in post-surgical lymphedema (**Stewart-Treves Syndrome**)
- Treatment is aggressive resection with wide margins and chemotherapy
- Poor prognosis with a 30% survival rate at 5 years
- IHC: **vascular markers** and **frequent keratins**
- Molecular: High-level amplification of MYC

Path Presenter

IHC: MYC



Spider-leg chromatin

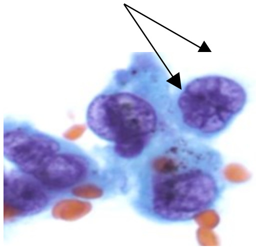
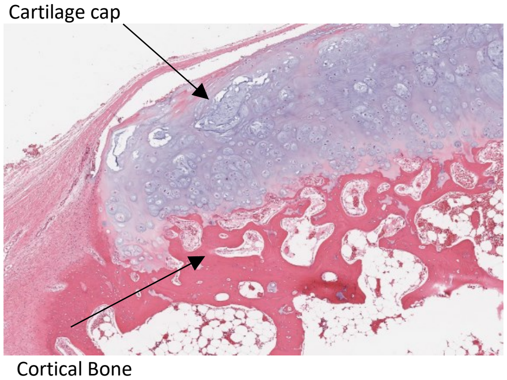
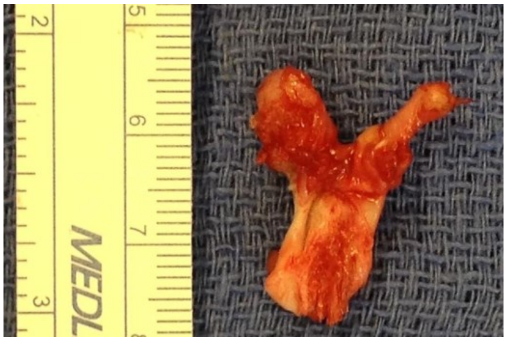


Image by: Dr. Terrance Lynn,

CARTILAGE/CHONDROBLASTIC TUMORS





Tibial Osteochondroma by: Paigeblue08

OSTEOCHONDROMA

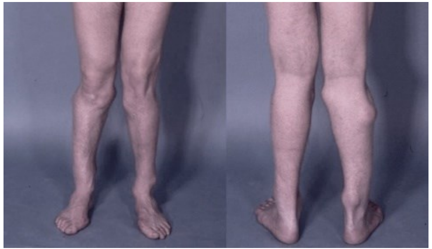
MORPHOLOGY

- **Cartilage cap** with growth plate-like architecture
- **Underlying** stalk with **medullary and cortical bone**
- No significant nuclear atypia or mitotic activity

OTHER HIGH YIELD POINTS

- **Most common bone tumor** and **occurs** largely in **first 2 decades**
- Usually in **metaphysis of distal femur**, **proximal tibia**, or **proximal humerus**
    - ➢ Due to enchondral ossification (bones pre-formed by cartilage)
- **Hereditary osteochondromatosis:**
    - ➢ Autosomal dominant inheritance
    - ➢ Germline mutation in EXT1 (8q24.1), EXT2 (11p11-12), EXT3 (19p)

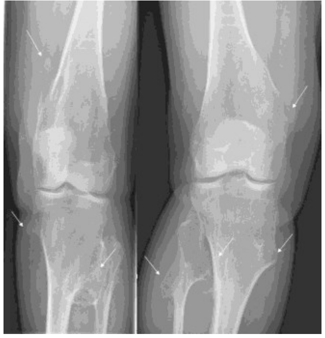
Clinical Images of MO



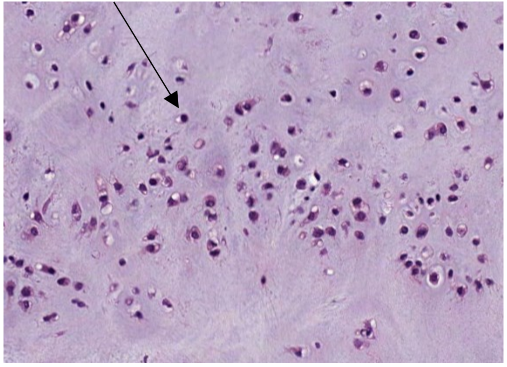
Images provided by: Dr. Judith VMG Bovee

Path Presenter

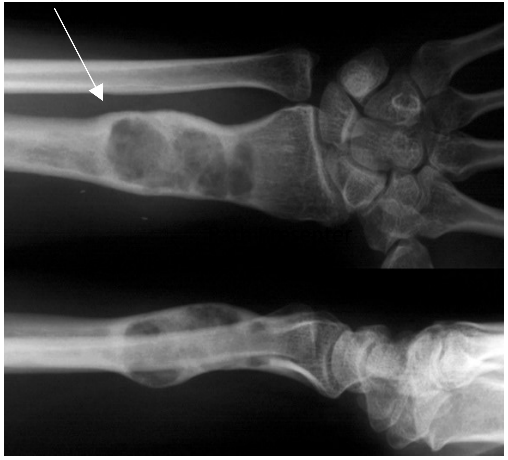
Multiple Osteochondromas



Provided by: Michielvds on Wikimedia



Chondrocytes with bland lymphocyte-like nuclei



Radiograph of patient with Ollier Disease

Radiograph courtesy of: Dr. Hellerhoff

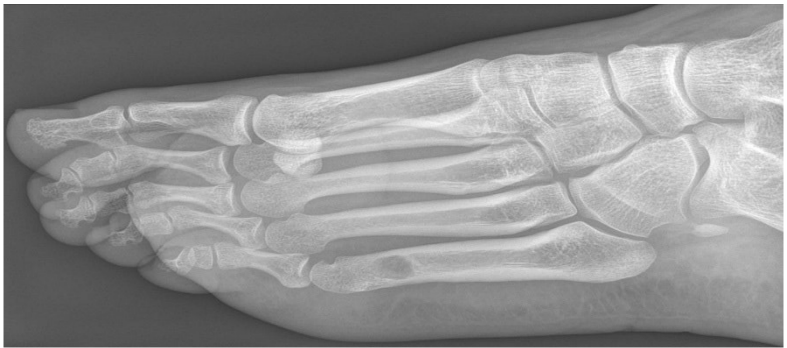
ENCHONDROMA

MORPHOLOGY

- Hypocellular, abundant hyaline cartilaginous matrix
- **Chondrocytes** in sharp-edged lacunae with **bland lymphocyte-like nuclei**
- No significant cytologic atypia, mitoses, cortical invasion, or soft tissue extension
- In small bones of hand, can have increased cellularity, myxoid cartilage, mild atypia and binucleation

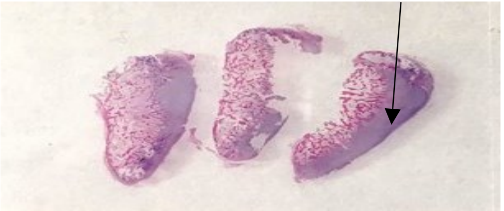
OTHER HIGH YIELD POINTS

- Benign, relatively common
- Hyaline cartilage neoplasm arising within the medullary cavity
- Most frequently in short tubular bones of the hands, often in the metaphysis
- Often treated with curettage, if symptomatic
- Molecular: Frequent IDH1 and IDH2 mutations,
  - Germline IDH1/ IDH2 mutations → Multiple enchondromas
    - Consider **Ollier disease** and **Mafucci Syndrome**

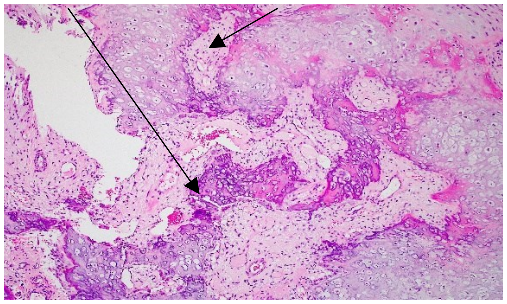


Radiograph courtesy of: Dr. Hellerhoff

Path Presenter



Cartilaginous cap



"Blue bone" Fibrotic trabeculae bone

Images courtesy of Dr. Syed T. Hoda; Twitter: @01sth02

BIZZARRE PAROSTEAL OSTEOCHONDROMATOUS PROLIFERATION (BPOP) *(also known as "Nora's Lesion")*

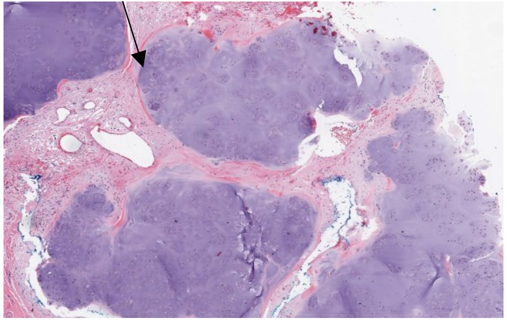
MORPHOLOGY

- **Benign surface lesion** composed of spindle cells, cartilage, and bone
- Not contiguous with medullary cavity
- Surrounded by **cartilaginous cap** with central trabecular bone (via endochondral ossification) and hypervascular bland spindle cells.
- Between the cartilage and bone is characteristic "**Blue bone**" with basophilia
- The **chondrocytes** can show **moderate atypia**
- **Mitoses may be numerous** but are **not atypical**

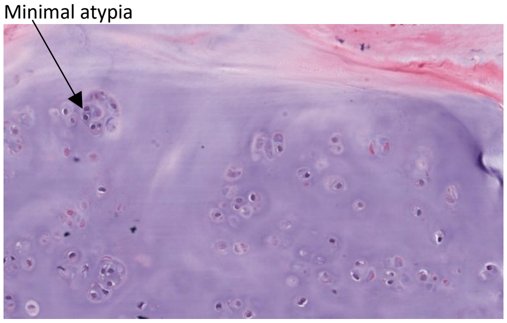
OTHER HIGH YIELD POINTS

- **Rare** and the **exact incidence** is **unknown**
- **Most common** in **small bones** of the **hand** and **feet**, often phalanges
- Presents as a **mass** which **may be painful** or **cause bleeding** if the mass distorts the nail architecture
- Unclear if it is a reactive process or neoplasm but can be locally aggressive
- **Recurrence is common** in nearly half of all cases
- **Radiography**: **Pedunculated** and **well-delineated mass** that is **radiolucent early on** and then **becomes** more **radiodense**

Multiple hyaline cartilage nodules



Minimal atypia



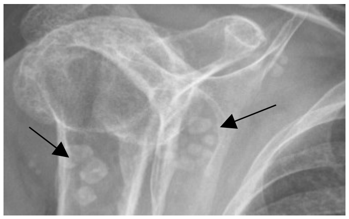
SYNOVIAL CHONDROMATOSIS

MORPHOLOGY

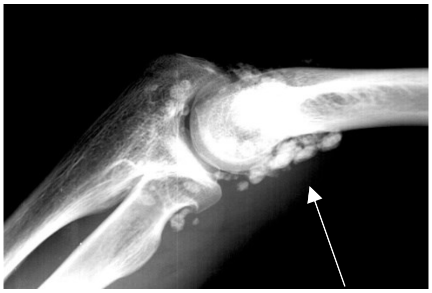
- **Multiple hyaline cartilage nodules** within synovium or loose joint space, chondrocytes cluster together in groups
- **Minimal atypia** is seen in the chondrocytes
- If significant atypia seen including loss of chondrocyte clustering, bone invasion, increased mitoses – increased concern for malignant status

OTHER HIGH YIELD POINTS

- Rare and peak age is **5th decade** with a **2:1 male to female** predominance
- Locally aggressive and can be multifocal
- Involves **large joints** (**knee is most common**) but can involve any joint
- **Molecular**: **FN1-ACVR2A** fusions



Radiograph By: Hellerhoff Wikimedia



Radiograph courtesy: Nat Folk on Wikimedia

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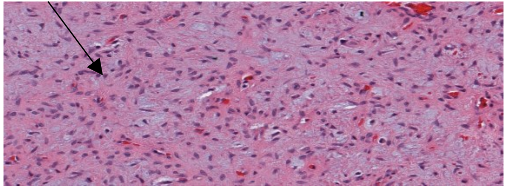
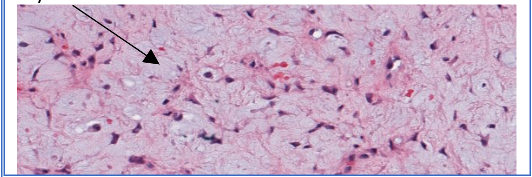
Stellate cells in chondromyxoid matrix



Myxoid stroma



CHONDROMYXOID FIBROMA

MORPHOLOGY

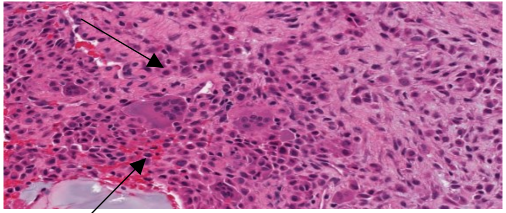
- Benign **lobulated lesion** with sharp margins
- Chondroid and **stellate cells** embedded in a chondromyxoid matrix
- Peripheral spindled cells and admixed giant cells

OTHER HIGH YIELD POINTS

- Benign lesion and typically seen in young adults
- Occurs in many sites, but often long bones near the knee
- Most arise within the medullary space and are frequently eccentric
- Treatment is variable based on location (curettage, en bloc resection)
- Radiograph: Multiloculated radiolucent lesion with a sharp sclerotic rim
- IHC: + S100 diffusely (like all cartilage)
- **Molecular: GRM1** fusions/upregulation

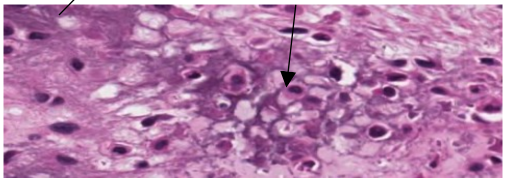
Path Presenter

Polygonal cells



Giant Cells

Chicken wire-like calcification



CHONDROBLASTOMA

MORPHOLOGY

- Sheets of ovoid to **polygonal cells** with a single grooved nucleus and eosinophilic cytoplasm and interspersed multinucleated giant cells
- Characteristic "**lace-like**" or "**chicken wire-like" calcification**
- Islands of **eosinophilic chondroid** matrix
- Can have **cystic degeneration**, **nuclear atypia**, and **mitoses**

OTHER HIGH YIELD POINTS

- **Benign tumor** and is seen in first and second decade, more common in **males**
- Involves the **epiphysis of long bones**, **most common** in **femur**
- **Radiograph:** Radiolucent lesion with well-defined sclerotic margin
- **IHC:** Positive for **H3F3 K36M**, **S100**, **SOX9**, **DOG1**
- Molecular: **H3.3 K36M** substitution (similar histone to GCT of bone)

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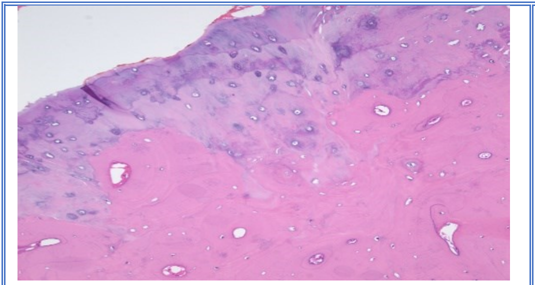


Image courtesy of Dr. Bonnie Balzer

SUBUNGUAL EXOSTOSIS

MORPHOLOGY

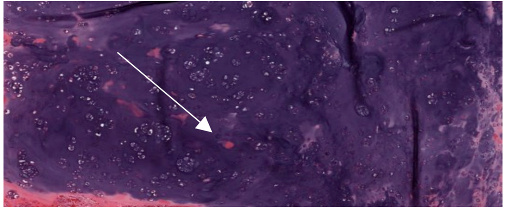
- **Benign osteocartilaginous surface lesion** in the distal phalangeal bone underneath the nail bed, most often big toe
- Sometimes cartilage is mildly atypical with mitoses
- No continuity with medullary cavity (as is seen in osteochondromas)

OTHER HIGH YIELD POINTS

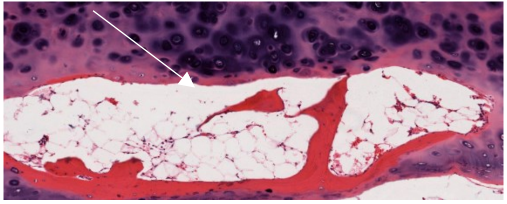
- Often young adults
- **Cytogenetics:** Recurrent breakpoint resulting in increased IRS4 expression

Path Presenter

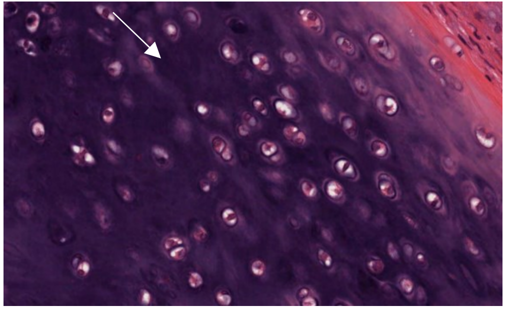
Abundant cartilaginous matrix (hyaline/myxoid)



Bone entrapment



Increased cellularity, bland



CONVENTIONAL CHONDROSARCOMA

MORPHOLOGY

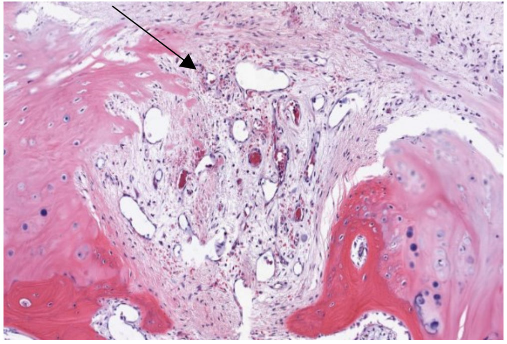
- **Abundant** cartilaginous matrix (**hyaline/myxoid**)
- Lobular growth, **entrapment** of pre-existing **bone**
- **Increased cellularity**, but **bland** condensed nuclei, variable binucleation
- No significant nuclear atypia or mitotic activity
    - **Grade 1: Hypocellular**, **nuclei** are **lymphocyte-like**
    - **Grade 2:** More **cellular**, **nuclei** are **large** with **irregular contours** and have **coarse chromatin**, mitoses infrequent
    - **Grade 3: Hypercellular**, **severe pleomorphism** and mitoses, and cells often more spindled

OTHER HIGH YIELD POINTS

- Macroscopic Features
    - **Central:** arising in the **medulla** of the bone
    - **Central primary: no** pre-existing **precursor**
    - **Central secondary: arising** from an **enchondroma**
    - **Secondary peripheral: arising in** pre-existing **cartilaginous cap** of an **osteochondroma** (cap > 2cm)
- Appendicular skeleton (easier to resect) → atypical cartilaginous tumor
- Axial skeleton (harder to resect) = chondrosarcoma, grade 1
- **Molecular**: ~50% have **IDH1 or 2 mutations** (likely progressed from **enchondroma**)
    - **Higher-grade** tumors have **TP53, RB1, CDKN2A mutations**

Path Presenter

Abrupt transition from cartilage to non-cartilage



DEDIFFERENTIATED CHONDROSARCOMA

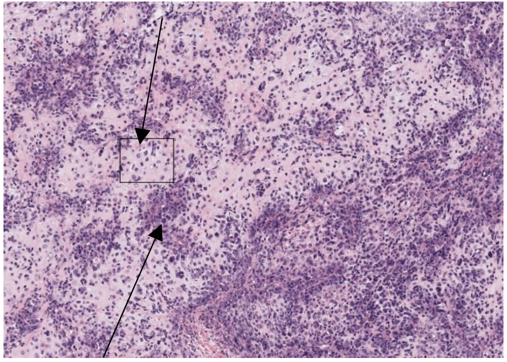
MORPHOLOGY

- Conventional chondrosarcoma with an **abrupt transition** to high-grade non-cartilaginous sarcoma

OTHER HIGH YIELD POINTS

- Seen in middle aged to elderly adults and develops in pelvis, or femur
- Very poor prognosis
- **Cytogenetics:** complex karyotypes
- **Molecular:** Frequent **IDH1/2** and **TP53** mutations

Path Presenter


Islands of organized hyaline cartilage
Undifferentiated component

MESENCHYMAL CHONDROSARCOMA

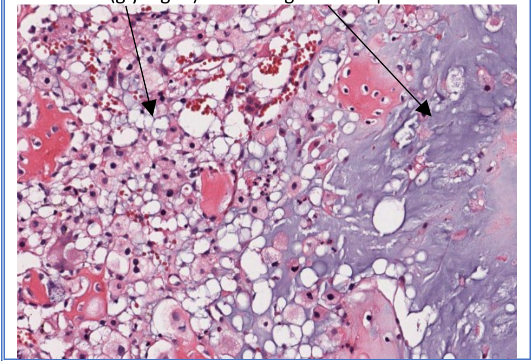
MORPHOLOGY

- Biphasic tumor with:
  - Islands of **organized hyaline cartilage**
  - **Undifferentiated component** with high nuclear to cytoplasm ratios
  - Frequent **staghorn vessels**

OTHER HIGH YIELD POINTS

- Aggressive and seen in young adults and adolescents
- Most often arises in craniofacial area (predilection for jaw)
- IHC: **Positive** for **S100**, CD99, **SOX9**, NKX2.2 (~70%), and vimentin
- **Molecular**: **HEY1-NCOA2** fusions (90%), IRF2BP2-CDX1 fusion

Path Presenter



CLEAR CELL CHONDROSARCOMA

MORPHOLOGY

- **Clear cells** centrally placed nuclei, abundant **glycogen-rich** cytoplasm, and **well-defined** cytoplasmic **borders**
- Woven bone and osteoclast-like giant cells
- Minimal atypia and low mitotic activity
- Half of cases have conventional **low-grade chondrosarcoma component**

OTHER HIGH YIELD POINTS

- Low-grade malignancy that is seen in adults in 4th decade
- Usually effects the epiphysis or apophysis of long tubular bones
- IHC: strong **S100** in clear cells

Path Presenter

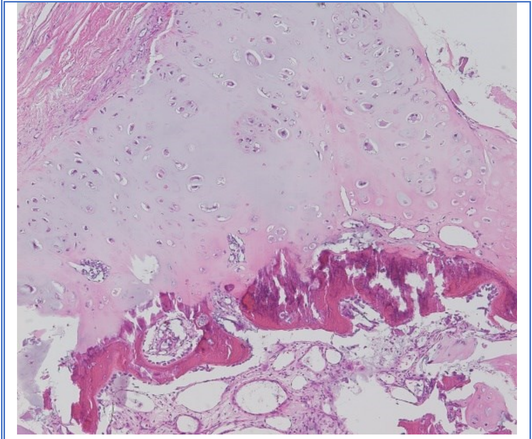


Image courtesy of Dr. Bonnie Balzer

PERIOSTEAL CHONDROSARCOMA

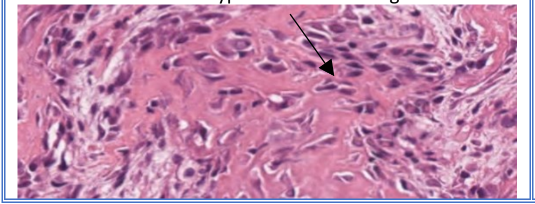
MORPHOLOGY

- **Cartilaginous tumor** on the surface of a bone with close association to periosteum with either:
  - Invasion of the underlying bone, or size >5.0 cm

OTHER HIGH YIELD POINTS

- **Located on the surface** of **long tubular bones**, usually the **distal femur**
- **Low metastatic rate**, grading not predictive
- **Molecular:** comparatively low IDH1/2 mutation rate
- **Differential diagnosis: Periosteal Chondroma**
  - Well-marginated, lobulated cartilaginous tumor arising on the bone surface, with elevation of the periosteum and erosion, but no invasion of the underlying bone cortex
  - Low to moderate cellularity, and relatively uniform chondrocytes
  - Usually <5 cm, benign, and treated with curettage
  - Frequently also has IDH1 mutations

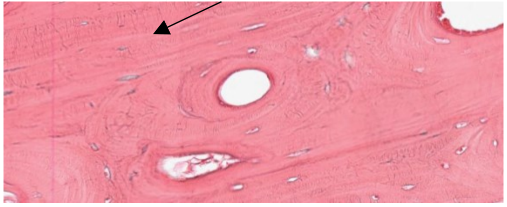
BONE LESIONS

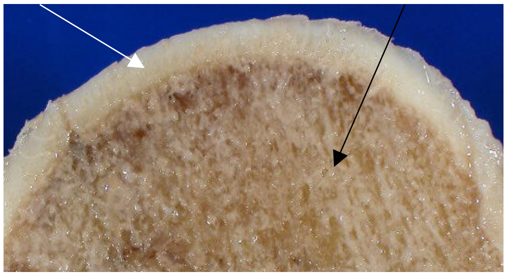


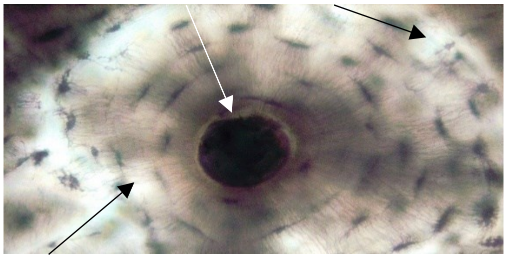
NORMAL BONE

MORPHOLOGY

- **Two main types of bone organization** (highlighted by polarization)
  - **Immature** → haphazard arrangement
  - **Mature** → parallel arrangement
- **Woven bone (Immature):**
  - Collagen fibers are **haphazardly arranged**


Lamellar bone
parallel collagen
Hypocellular


Cortical bone
Trabecular bone

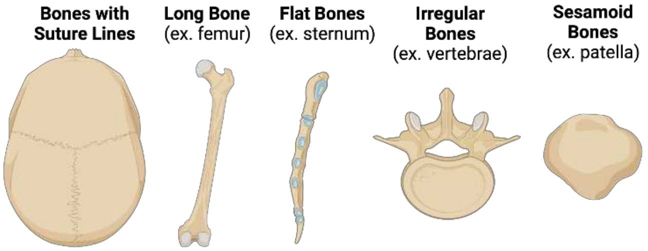

Osteon
Haversian canal
Lamellae
Canaliculi

- ➢ **Formed during ossification** and **rapid bone growth**/repair
  - ▪ Example: fracture callus
- ➢ Relatively **hypercellular** with **large cells**

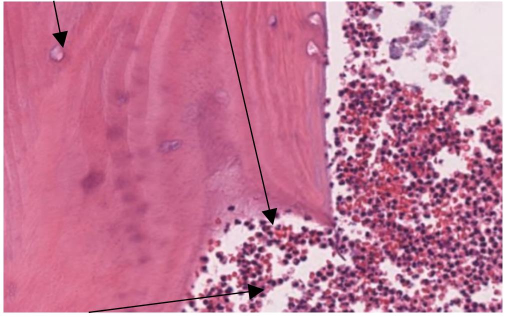
- **Lamellar bone (Mature):**
  - ➢ Collagen fibers are organized in **parallel arrays**
  - ➢ Formed through **gradual remodeling** of woven bone
  - ➢ In adults, almost all bone is lamellar
  - ➢ **Hypocellular** with **small cells**
- Two main types of mature lamellar bone architecture:
  - ➢ **Cortical (Compact) Bone:** Dense lamellar bone with Haversian canals surrounded by concentric lamellar units
  - ➢ **Trabecular (Cancellous) Bone:** Connecting plates of lamellar bone

OTHER HIGH YIELD POINTS

- **Tumor Bone:** Typically, woven bone; either mineralized or unmineralized
- Deciding if it is bone/osteoid (unmineralized bone) versus collagen versus extracellular material
  - ➢ "Cement lines" (reversal lines)→ Thin, dark, linear lines are seen in osteoid, but not other substances (specific, but not sensitive)
  - ➢ SATB2 → expression supports osteoblastic differentiation


Bones with Suture Lines
Long Bone (ex. femur)
Flat Bones (ex. sternum)
Irregular Bones (ex. vertebrae)
Sesamoid Bones (ex. patella)

BONE AND JOINT INFECTIONS


Empty lacunae
"Moth Eaten"
Abundant neutrophils

ACUTE OSTEOMYELITIS

MORPHOLOGY

- **Necrotic bone** with **empty** osteocyte **lacunae**
- May see brisk osteoclast activity
- Bone often appears "**moth eaten**" (irregular erosions) with lots of "**rat bites**"

OTHER HIGH YIELD POINTS

- Often caused by **bacteria** (usually Staphylococcus)
- Can get from **hematogenous spread** ("**primary**," often in kids in **metaphysis** of **long bones** or adults in spine)
- Can also be from **direct inoculation**, often from trauma or ulceration ("**secondary**," often **adults**)

Path Presenter

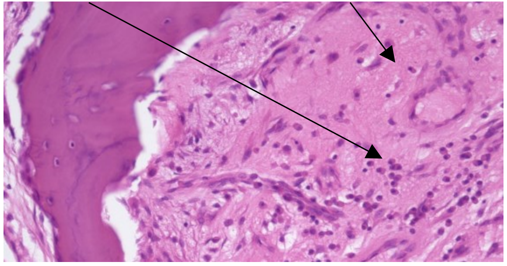

Plasma cells and lymphocytes
Fibrosis

Image courtesy of Dr. Bonnie Balzer

CHRONIC OSTEOMYELITIS

MORPHOLOGY

- **Chronic inflammation with bone destruction**
- Marrow replaced by **fibrosis** with plasma cells and lymphocytes
- Often bone remodeling with osteoclasts and osteoblasts
- Similar irregular **rat/moth-eaten appearance**

OTHER HIGH YIELD POINTS

- **Necrotizing granulomas** → consider **Tuberculosis** ("**Pott's disease**" in spine)
- Can have sinus tract to surface lined by squamous epithelium → can turn into squamous cell carcinoma

Path Presenter

8. BONE AND SOFT TISSUE PATHOLOGY

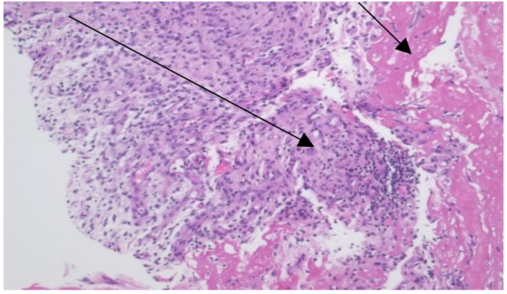


Image courtesy of Dr. Bonnie Balzer

SEPTIC ARTHRITIS

MORPHOLOGY

- **Neutrophilic inflammation** of synovium with accumulation of **purulent debris** in joint space
- **Necrosis** and **fibrin strips**

OTHER HIGH YIELD POINTS

- Often clinical/lab diagnosis
- Caused by **bacteria**, often **Staphylococcus** (**S. epidermidis** with **prostheses**)
- Leads to **rapid cartilage destruction** → acute medical emergency that needs rapid treatment

Path Presenter

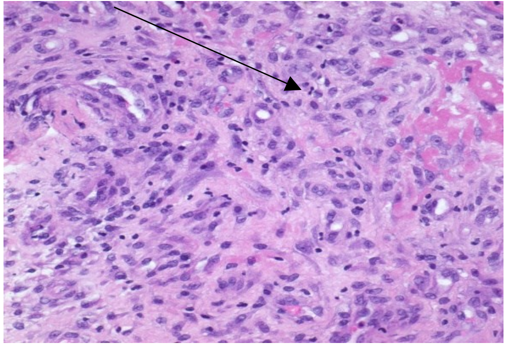


Image courtesy of Dr. Bonnie Balzer

PERIPROSTHETIC JOINT INFECTION

MORPHOLOGY

- If there is a concern for infection, will often send joint capsule for frozen section neutrophil count
  - **Cutoff >5 neutrophils/HPF in 5 separate HPFs**, exclude surface fibrin
- Be SURE that it is PMNs → lymphocytes can be twisty and mimic PMNs

OTHER HIGH YIELD POINTS

- Can cause **prosthetic loosening**, requiring **revision arthroplasty**
- **Treatment** → **prosthesis removal** and subsequent reimplantation after eradication of the infection (may take weeks)
- Also evaluated clinically based on physical exam, culture, ESR, CRP, and synovial fluid studies

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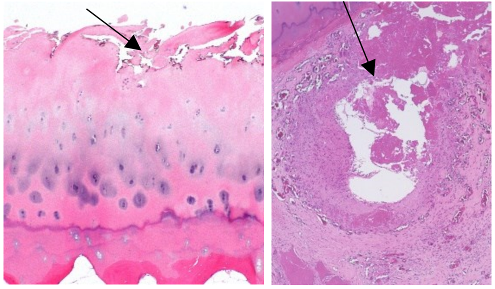
DEGENERATIVE/REPARATIVE CHANGES



Courtesy of Dr. Michael Bonert & Dr. Bonnie Balzer

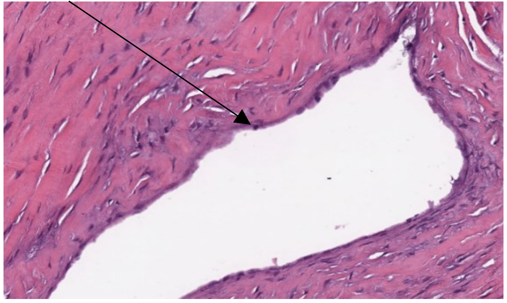
DEGENERATIVE JOINT DISEASE

MORPHOLOGY

- Non-inflammatory **loss of joint cartilage**, **subchondral bone sclerosis**, periarticular **bone cysts** (Geodes), **osteophyte formation**, and **synoviocyte hypertrophy/hyperplasia**

OTHER HIGH YIELD POINTS

- Also known as "DJD" or Osteoarthritis ("OA")
- Typically seen in **older individuals**
- Common result of a variety of factors including trauma, "**wear and tear**," **metabolic diseases**, **avascular bone necrosis**, and **altered loading/anatomy**
- If treated surgically → joint arthroplasty



GANGLION CYST

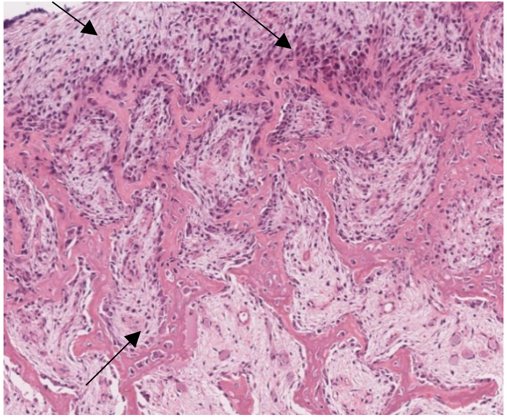
MORPHOLOGY

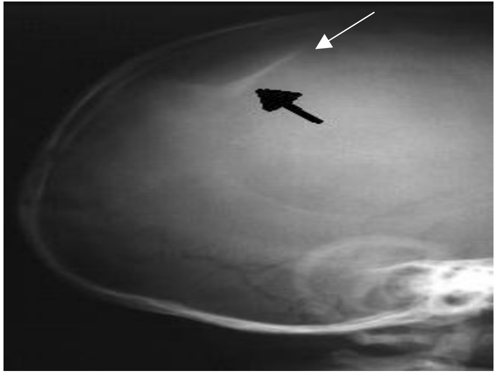
- Cysts composed of fibrous tissue **without a lining**
- Contain **myxoid/mucous material**
- Can be **unilocular** or **multilocular**

OTHER HIGH YIELD POINTS

- Most common in young adults
- Usually occurs most often on **wrists** and **hand/feet**

Path Presenter





Radiograph provided by: A. E. Francis at the NIH

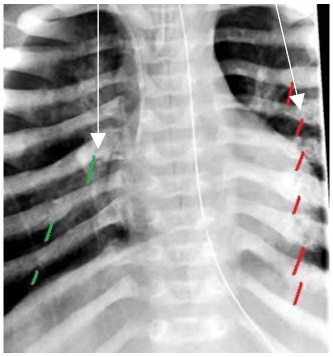
FRACTURE CALLUS

MORPHOLOGY

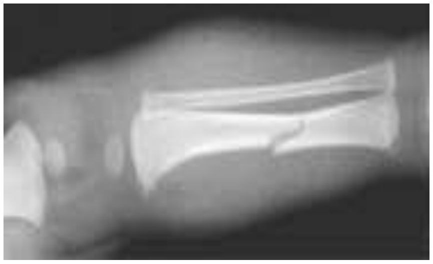
- Reparative changes seen at a site of prior bone fracture
- Stages to fracture repair:
  - **Stage 1: Hemorrhage** and **hematoma**
  - **Stage 2: Fibrocartilagenous matrix** forming a “soft callus”
  - **Stage 3:** Creation of a woven bony matrix by **osteoblastic rimming**
  - **Stage 4: Bone resorption** by multinucleated osteoclasts
- **Should NOT see atypical mitoses**, significant cytologic pleomorphism

OTHER HIGH YIELD POINTS

- In children, these findings should **raise suspicious for child abuse**
  - **Multiple fractures** at **different stages** of **healing**
  - **Pre-ambulatory children** and infants with **femur fractures**
  - **Fractures** to **ribs**, **skull**, or **scapula**
  - “**Bucket handle**” fractures or “**nightstick**” midshaft **fracture**



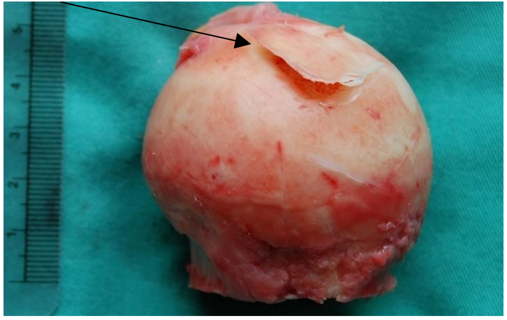
Spiral fracture of Tibia



Path Presenter

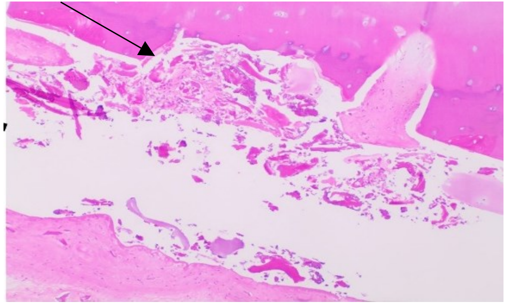
Radiographs provided by: A. E. Francis at the NIH

“Crescent sign” of articular cartilage separation



Courtesy of Dr. Steven Fruitsmaak, MD, PhD

Cartilage loosening



Courtesy of Dr. Mikael Häggström

AVASCULAR NECROSIS (ASEPTIC NECROSIS)

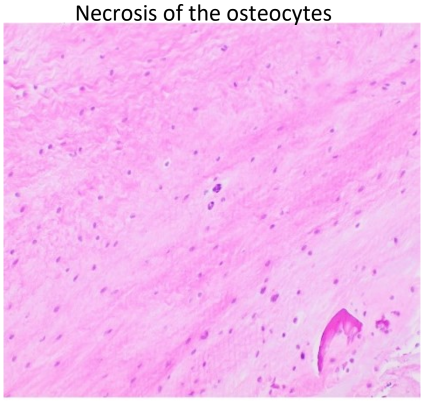
MORPHOLOGY

- Geographic area of **subchondral bone and marrow necrosis** with partially **separated articular cartilage** surface **(“crescent sign”)**
- **Empty** osteocyte **lacunae**
- **Necrosis** throughout

OTHER HIGH YIELD POINTS

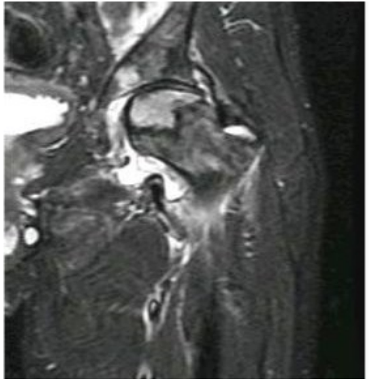
- **Risk factors: Sickle cell disease**, trauma, **steroids**, **alcohol**, **chemotherapy**, **collagen vascular disease**, pregnancy, **coagulopathy**, **cancer**, etc.

Necrosis of the osteocytes



Courtesy of Dr. Mikael Häggström

Avascular Necrosis Femoral Head



Courtesy of Dr. Jordi March I Nogue, MD

Pigmented debris in histiocytes

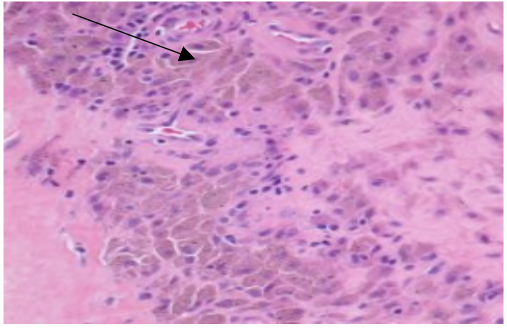


Image courtesy of Dr. Bonnie Balzer

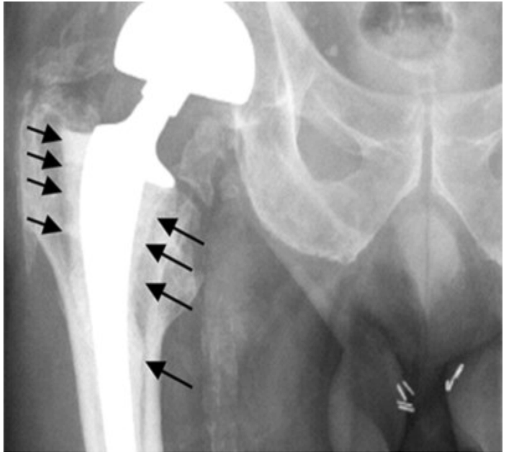


Photo courtesy of Zhenxin Shen et al.

ASEPTIC JOINT LOOSENING

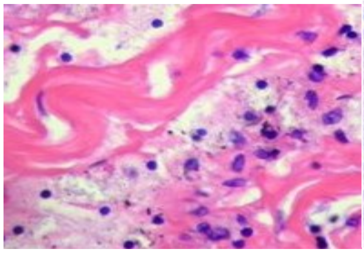
MORPHOLOGY

- **Foreign material wear particles**
  - Fragments of **prosthetic material** that have broken off including **metal**, **polyethylene glycol**, **cement**, **ceramic**
- **Ingested by macrophages** → causes **inflammation** around joint → **osteolysis** and **joint loosening** around prosthesis
- Abundant **foamy histiocytes**, foreign body **giant cells**, and **inorganic particles**
- Particles from metal articular surfaces are small and appear black
- **Accumulate in macrophages** and fibrous tissue→ **"Metallosis"**

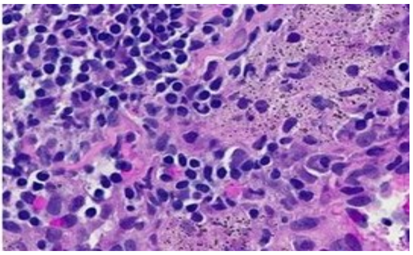
OTHER HIGH YIELD POINTS

- Metal can even make its way to regional lymph nodes
- **Aseptic Lymphocytic Vasculitis-associated Lesion (ALVAL)**
  - Seen with metal-on-metal articulation occur
  - Despite name, no true vasculitis is present
  - Three defining features:
    - **Prominent lymphoid aggregates**, often near venules
    - **Absence** of **obvious metal debris**
    - **Necrosis** of synovium

Metallic debris

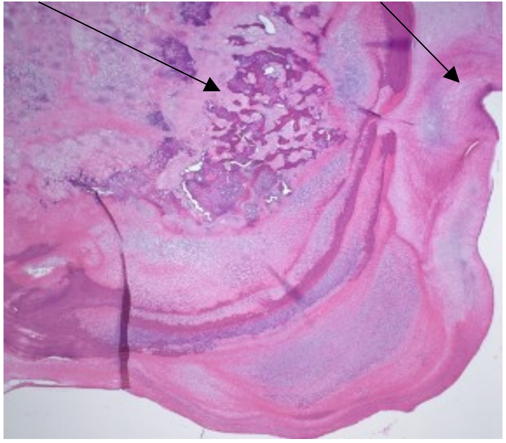


Metallic debris



Courtesy of Dr. Frank Ingram

Cartilage Laminated fibrin



Courtesy of Dr. Bonnie Balzer, MD

LOOSE BODIES

MORPHOLOGY

- Fibrinous Loose bodies ("**Rice Bodies**")
  - Consist of **laminated fibrin**
  - Grossly resemble **rice grains**
- **Osteochondral** or **Cartilaginous Loose bodies**
  - Detached fragments of **articular cartilage** with or without bone
  - Result from trauma and often **solitary**

OTHER HIGH YIELD POINTS

- Loose **fragments** of **tissue** found **free within** the **joint space**
- Can result from trauma, degenerative joint disease, or neoplasm
- Most common in knee → cause locking and pain
- Related entity: **Synovial Chondromatosis**
  - **Multiple hyaline cartilage** nodules in a synovium or loose in joint space
  - Chondrocytes cluster together in groups
  - **Molecular**: FN1-ACVR2A fusions

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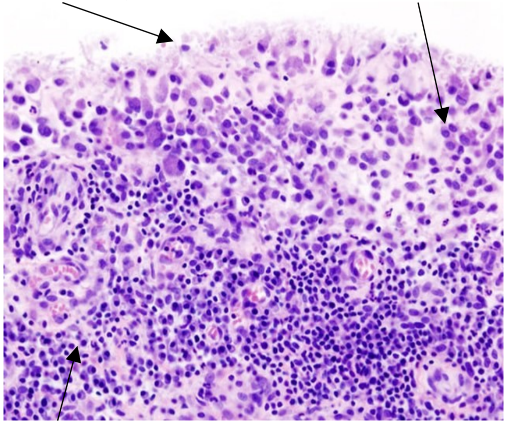
8. BONE AND SOFT TISSUE PATHOLOGY

AUTOIMMUNE DISEASES



RHEUMATOID ARTHRITIS

MORPHOLOGY

Related entities

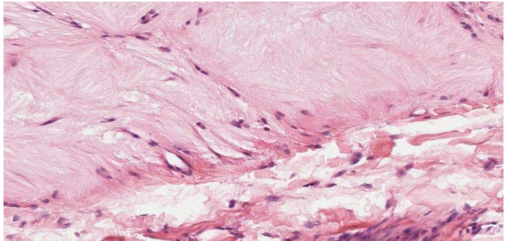
- **Chronic Synovitis:** Expands synovium with chronic inflammation (lymphocytes and plasma cells), often with lymphoid aggregates
  - Often reactive/hyperplastic synovium with surface fibrin/fibrinoid necrosis and granulation tissue
- **Pannus:** Synovium that erodes cartilage and other joint structures → characteristic marginal erosions of bone on X-ray
- **Rheumatoid nodule**: Necrotizing granulomas with central necrobiosis

OTHER HIGH YIELD POINTS

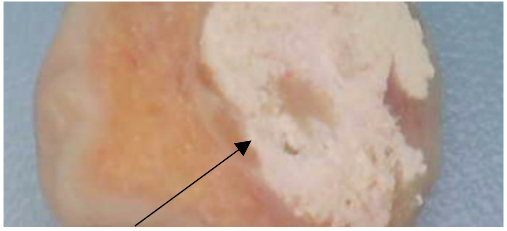
- **Most common primary** inflammatory **arthropathy**
- Chronic, idiopathic **erosive symmetric polyarthropathy**
- **Impacts all joints**, but worst impacted are small joints of hands
- Many extra-articular manifestations (e.g., Lung disease)
- Serology: **Positive Rheumatoid Factor (RF)**

CRYSTALLINE DISEASES

Fluffy pink deposits



Gout affecting first MTP joint



Gross examination of gout

GOUT

MORPHOLOGY

- **Fluffy pink deposits** with associated granulomatous inflammation
- Can have **scattered giant cells** surrounding deposits
- Joint fluid often **neutrophil-rich**
- Uric acid dissolves in water during staining process (not seen on H&E slides)
- Fresh touch preparations or unstained slides → **"needle-shaped" yellow, negatively birefringent crystals**

OTHER HIGH YIELD POINTS

- Usually seen in males
- Most common joint: **1st MTP**
- Presents as a very painful nodule

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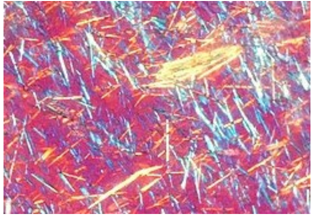
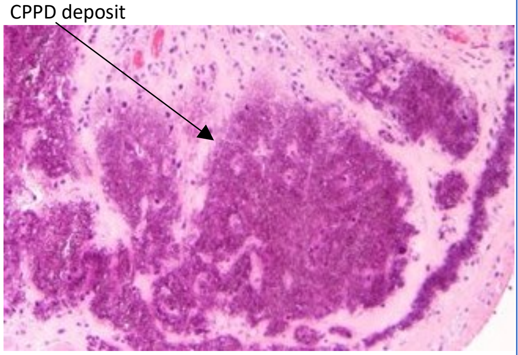
Negatively Birefringent



Courtesy of: Dr. Jeff Cloutier

CPPD deposit



Images courtesy of Dr. H. Yang (Twitter: @HENRYY_MD)

PSEUDOGOUT

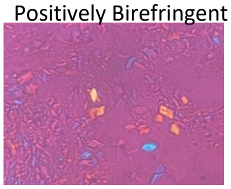
MORPHOLOGY

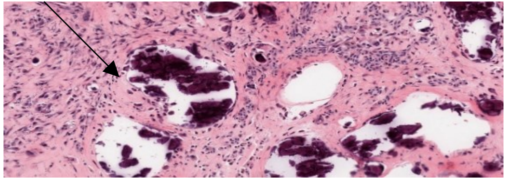
- **Calcium Pyrophosphate Dihydrate (CPPD) deposits** in **cartilage** and in the soft tissue of the **joint**
- **Rhomboidal** purple-blue **positively birefringent crystals**
- **Well-demarcated basophilic material** with virtually **no inflammatory response**

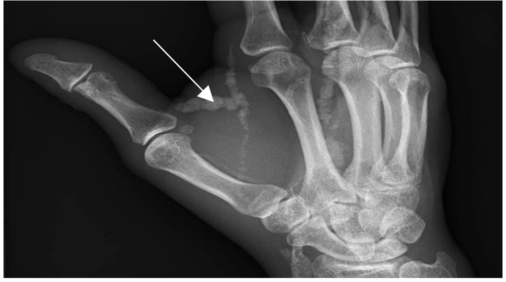
OTHER HIGH YIELD POINTS

- Often associated with degenerative joint disease
- Often incidental finding in arthroplasty finding
- Crystals found inside leukocytes

Positively Birefringent






Radiograph courtesy of: Jto410 (Radiologist)

TUMORAL CALCINOSIS

MORPHOLOGY

- **Calcium hydroxyapatite deposits in** the **soft tissue**
- Lobules of **apatite-type calcifications** surrounded by **chronic inflammation** with a prominent **foreign body giant** cell reaction

OTHER HIGH YIELD POINTS

- Common locations: **hands**, **shoulder**, **sites of pressure**
- **Idiopathic/Sporadic** tumoral calcinosis (**most common**)
  - Seen in **ages < 20** and is usually painless
- Secondary tumoral calcinosis is trauma or due to a systemic disorder
  - **Renal failure** and on **dialysis** → electrolyte abnormalities
- **Familial tumoral calcinosis:** genetic-related
  - **Autosomal recessive,** more **common** in **African Americans**
  - **Hyperphosphatemia type:** Mutations in FGF23, KL, or GALNT3 genes
  - **Normophosphatemia type:** Mutations in SAMD9 gene

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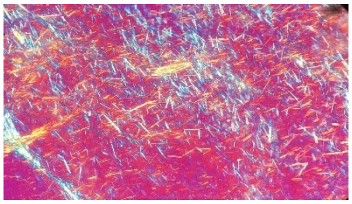
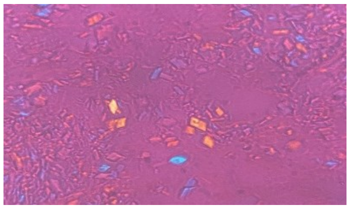
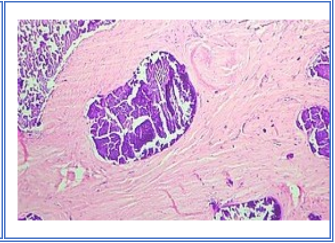
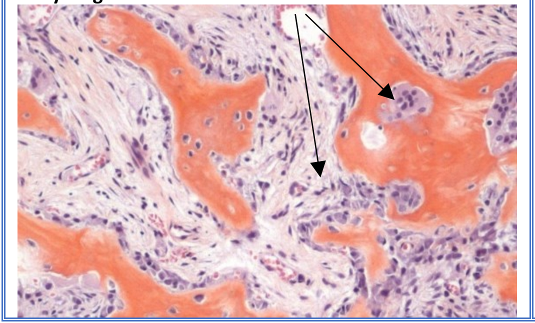
SUMMARY OF CRYSTALLINE DISEASES

	Gout	**Pseudogout**	**Tumoral calcinosis**
Age	Middle age	Older	Young
Site	1st MTP	Knee	Shoulder, Hips
Crystal Shape	Needle	Rhomboid	Irregular gritty plates
Type	Uric acid	Calcium pyrophosphate	Calcium hydroxyapatite
Polarizable	Yes **Negative Birefringent**	Yes, **Positive birefringent**	**No**
Seen on H&E	**No**	Yes	Yes
Inflammatory reaction	Yes	**No**	Yes
Image			

METABOLIC/ENDOCRINE/IDIOPATHIC BONE LESIONS

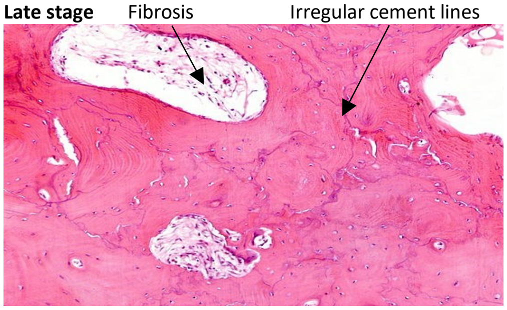


PAGET DISEASE

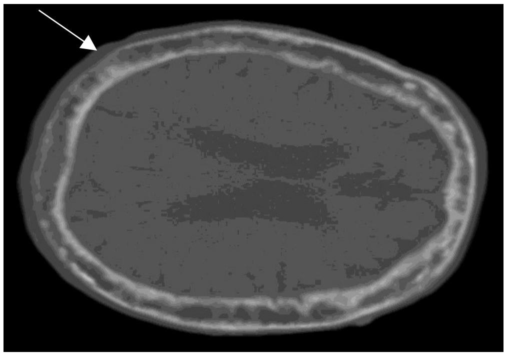
MORPHOLOGY

- Localized **disorder of bone remodeling** characterized by focal areas of **increased turnover** with excess bone synthesis and resorption
- Unusually **large osteoclasts** with increased nuclei and prominent nucleoli
- Prominent **osteoblastic rimming**
- Paratrabecular **marrow fibrosis**
- Unusually thick and thin bone trabeculae
- Numerous irregular **reversal cement lines** and **bone scalloping**
- Mosaic pattern
- **Histology** is **variable** based on stage of disease

Courtesy of Dr. Raul Perret, MD (Twitter: @kells108)



Thickened calvarium



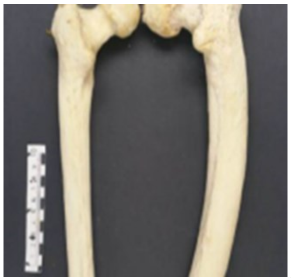
Courtesy of Dr. Laughlin Dawes

- ➢ **Early stage:** **more resorptive** and has **numerous osteoclasts**, **increased vascularity** and **resorptive** surfaces
- ➢ **Mid stage: more synthesis** due to **increased osteoblastic activity** and osteoclastic resorption (which slows)
- ➢ **End stage:** Extensively **sclerotic** bone

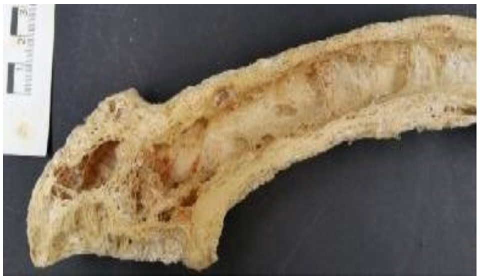
OTHER HIGH YIELD POINTS

- Etiology is unknown, does occur in clusters of families
- Often localized to a single bone (monostotic) in **elderly men**
- **Most common** sites are **pelvis**, femur, spine, and skull
- Monitoring of disease can be done using **Alkaline phosphatase**
- **Grossly,** bones can be **pumice (look like a sponge)** and have **thickened cortex**
- **Radiography:** can show "Blade of grass" sign or typical "cotton wool" or "ground glass" appearance due to osseous matrix synthesis
- **Familial cases** usually have **chromosomal abnormalities** and **autosomal dominant inheritance**
- **Confers** an **Increased risk** of **osteosarcoma**

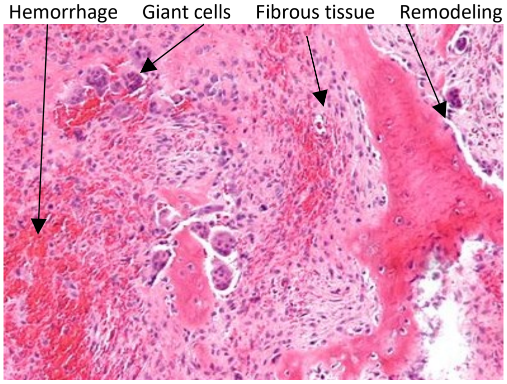
Deformed bone



Pumice appearance of bone

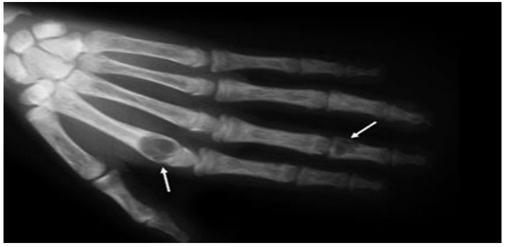


Photographs courtesy of Elena Nebot Valenzuela & peter Pietschmann



Courtesy of Dr. Michael Bonert, MD

Brown tumor on Radiograph



Radiograph courtesy of Dr. Frank Gaillard

BROWN TUMOR OF HYPERPARATHYROIDISM

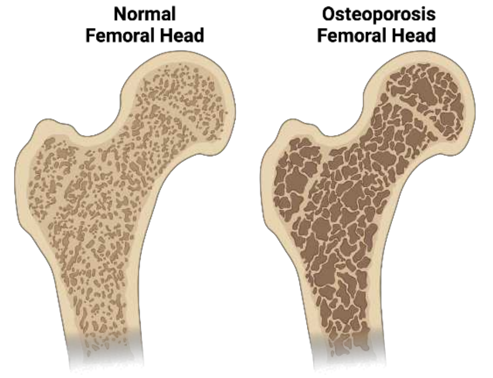
MORPHOLOGY

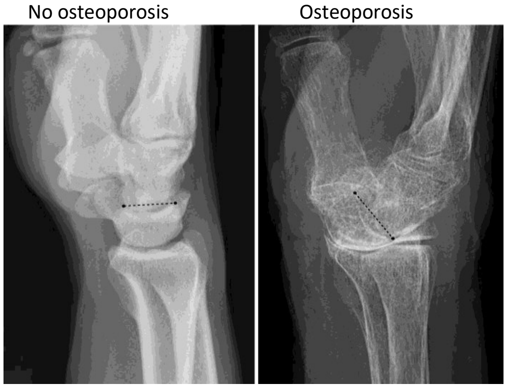
- Hemorrhage and extravasated **erythrocytes**
- **Hemosiderin-laden macrophages** and other inflammatory cells
- **Plump fibroblasts** and scattered **osteoclast-like giant cells**
- **Woven bone** with adjacent **fibrous tissue**

OTHER HIGH YIELD POINTS

- Usually seen in the **3rd to 4th decade** and **more common** in **females**
- Forms a **mass lesion** that **may be painful**
- May be **solitary** or involve **multiple bones**
- Frequently **arises** in **pelvis**, **clavicles** & ribs, or **extremities**
- **Radiology**: expansile **lytic lesion** which may have **trabeculations and may** have **well-defined margins**
- **Cause of lesion**: **Hyperparathyroidism**
  - ➢ **PTH binds** to surface **receptors** on **osteoblasts** → **RANKL** upregulated and **binds** to **RANK receptor** on **osteoclastic precursors** → **osteoclast development** and subsequent **resorption**
- Gross examination: Red-brown lobulated, hemorrhagic mass which expands (and thins) the bone cortex
  - ➢ May develop large**, blood-filled cysts** → **osteitis fibrosa cystica**
- **Biochemical test: PTH** and **serum calcium** will be **elevated**
- **Treatment**: parathyroidectomy → tumor will regress and new bone will form

8. BONE AND SOFT TISSUE PATHOLOGY





Courtesy of Dr. Nevit Dilmen and Dr. Mikael Häggström

OSTEOPOROSIS

MORPHOLOGY

- Cortical thinning and decreased bone volume
- Trabeculae are thin, lose their interconnections between each other, and have smooth contours (Trabeculae will be <10% of marrow area)
- May become fatty within the marrow space due to age related changes
- **Decrease in mass** of mineralized bone

OTHER HIGH YIELD POINTS

- **Primary osteoporosis:**
  - Frequent in **postmenopausal women**
  - **Mechanism**: **Decreased estrogen** acting on osteoclasts receptors → **decreased FASL induction**→ **osteoclasts** have **longer lifespan** due to decreased apoptosis
  - **Decreased bone density** usually takes **~10 years to notice**
  - **Risk factors:** low body weight, low BMI, low body fat (site of estrogen synthesis in post-menopausal), **smoking**, alcohol use
- **Secondary Osteoporosis:**
  - Usually caused by **systemic disorders** such as **malabsorption**, **hypothyroidism**, **hyperparathyroidism**, **hematologic** disorders, **corticosteroids**, **anti-hormonal medications**
- **Increased risk of fracture** over time**,** often **little force required** to cause
- **Gross examination**: Decreased bone mass → fragile
- **Radiology: DEXA Scan → T-score below 2.5 standard deviations below** normal aged-matched individuals

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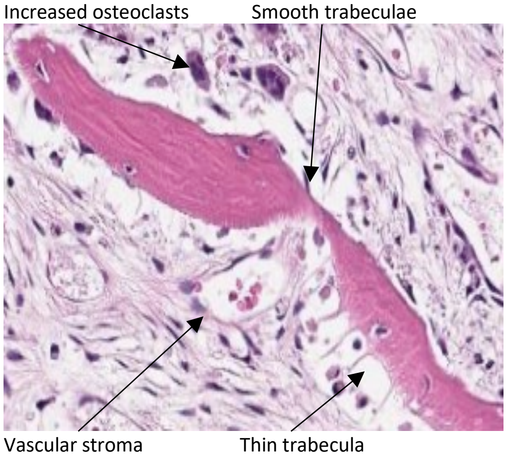


RENAL OSTEODYSTROPHY

MORPHOLOGY

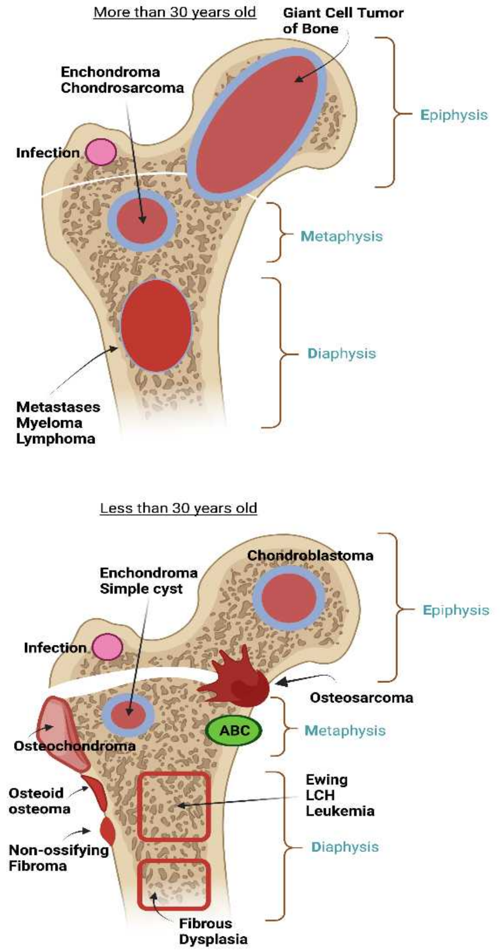
- **Trabeculae are smooth** and is generally **unmineralized**
- Marrow space will demonstrate a **vascular stromal fibrosis**
- Thinning of the cortical bone as osteoclast activity increases

OTHER HIGH YIELD POINTS

- Usually seen in individuals with renal failure and on dialysis
- With renal failure → **decreased phosphate excretion**, which will result in **decreased serum calcium** levels → **increased PTH** → kidney unresponsive → **hydroxylation** of 25-0H vitamin D3 is **impaired** → **osteoclastic activity increases**
- **Radiology: increased radiolucency, DEXA** will show **similar** findings **to osteoporosis**
- **Treatment**: Phosphate binders; overtreatment → adynamic renal osteodystrophy → no osteoid formation and nearly no cellular activity

8. BONE AND SOFT TISSUE PATHOLOGY

TUMORS OF THE BONE


More than 30 years old
Giant Cell Tumor of Bone
Enchondroma
Chondrosarcoma
Epiphysis
Infection
Metaphysis
Diaphysis
Metastases
Myeloma
Lymphoma
Less than 30 years old
Chondroblastoma
Enchondroma
Simple cyst
Epiphysis
Infection
Osteosarcoma
ABC
Metaphysis
Osteochondroma
Osteoid osteoma
Ewing
LCH
Leukemia
Non-ossifying Fibroma
Diaphysis
Fibrous Dysplasia

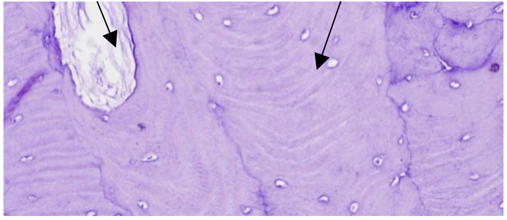
Images created by Dr. Kenechukwu Ojukwu via Biorender

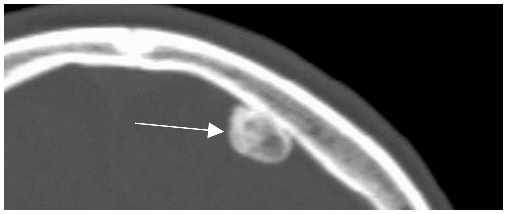
EPIDEMIOLOGY AND ANATOMIC SITES

- Overall, primary clinically significant bone tumors are rare
- Benign, incidental tumors (like non-ossifying fibroma) are relatively common, but are often clinically insignificant
- Primary bone sarcomas have a **bimodal** distribution:
  - **First peak in second decade (teens with actively growing skeleton):**
    - Osteosarcoma, Ewing sarcoma
  - **Second peak after age 60:**
    - Chondrosarcoma, Osteosarcoma
- Most common location is **near the knee**, which is the site of the fastest growing growth plate (although variable by tumor)
- Bone tumors are **most often de novo**
- **Risk-factors** that **predispose** an individual to **osteosarcoma**
  - Radiation, Paget's Disease of Bone, chronic osteomyelitis, bone infarctions, and prosthetic joints
- **Symptoms**: Often pain, which is classically worse at night, and a mass; Can have pathologic fractures, swelling, tenderness
- **Classic specific locations:**
  - **Anterior Cortex of Tibia:** Adamantinoma and osteofibrous dysplasia
  - **Posterior Cortex of Distal Femur:** Parosteal osteosarcoma
  - **Clivus, Vertebral bodies, Sacrum**: Chordoma
  - **Posterior Elements of Spine:** Osteoblastoma

Skeleton	Less than 30 years old	More than 30 years old
Axial (skull, vertebrae, pelvis)	Osteoblastoma, Langerhans cell histiocytosis, Aneurysmal bone cyst (ABC), Hemangioma	Metastases, Plasmacytoma, Hemangioma, Chordoma
Appendicular (arms and legs)	**Most tumors,** Osteosarcoma, Ewing sarcoma	**Most tumors,** Chondrosarcoma, Osteosarcoma
Acral (hands and feet)	Enchondroma	Enchondroma

OSTEOGENIC TUMORS


Inconspicuous osteoblasts
Lamellar bone


Radiodense

Imaging courtesy of: Dr. James Heilman, MD

OSTEOMA

MORPHOLOGY

- Composed of **lamellar/cortical-type bone with haversian-like systems**
- Inconspicuous osteoblasts
- May have a fibrous component → mimics a fibroosseous lesion

OTHER HIGH YIELD POINTS

- Benign tumor that is usually seen in middle-aged adults
- Usually occur on **face** or **jaw** bones → sites of membranous ossification
  - Most common is in **frontal** & **ethmoid sinuses**
  - Develops in medullary cavity→ called a "Bone Island"
- **Radiology:** Usually an incidental finding and is **uniformly radiodense**
- **Gross examination: Tan-white**, firm and usually <2 cm in size
- **Multiple osteomas** → consider **Gardner's syndrome** (subset of FAP)
- Generally, require no treatment unless symptomatic

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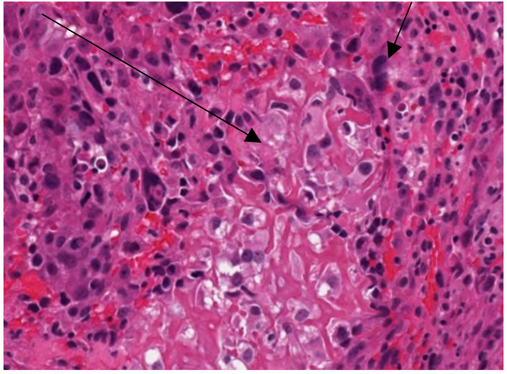

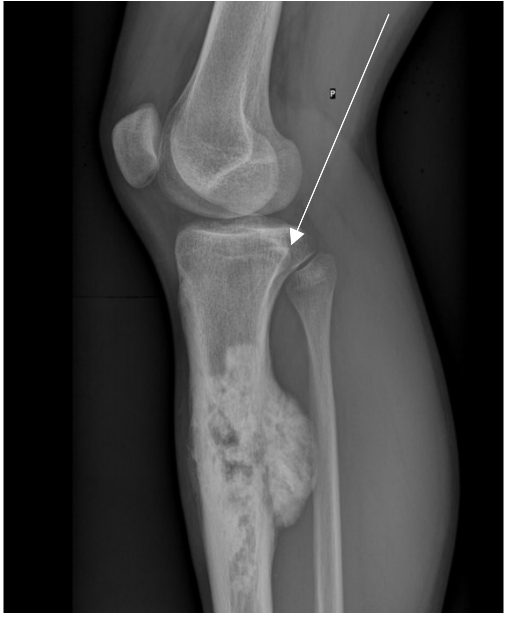

Radiograph courtesy ofL Dr. Yousef Samir

CONVENTIONAL OSTEOSARCOMA

MORPHOLOGY

- **High-grade** sarcoma in which tumor cells produce bone
- Requires **neoplastic bone** formation (any amount is sufficient for diagnosis)
- Woven bone will have disorganized trabeculae
- Has an infiltrative growth pattern
- **High-grade cytologic atypia** and "normalize" if surrounded by bone matrix
- Mitotic activity is brisk and has atypical forms
- Can have **various components**:
  - Cartilaginous (chondroblastic osteosarcoma)
  - Spindled cells (fibroblastic osteosarcoma)
  - Others: Giant cell-rich, telangiectatic, osteoblastoma-like

OTHER HIGH YIELD POINTS

- Usually seen in **ages 10-20** and **males** are **slightly more common**
- Most common to arise in long tubular bones
  - **Femur** > proximal tibia > proximal humerus
- Presents as a **painful**, **enlarging mass** and overlying skin may be erythematous
- **Metastasis** is **hematogenous** and most frequently to the **lung**
- **IHC: Positive** for **SATB2**, **CD99**, **S100** (cartilaginous areas); variable keratins
- **Molecular:** Typically arise de novo, but will have mutations in **RB1** and **TP53**
  - Chromosomal instability and abnormalities on karyotype
  - **MDM2 amplification** → arises from **low-grade central osteosarcoma**
  - Germline mutation in **RB1** → **Hereditary retinoblastoma**
  - Germline mutation in **TP53** → **Li-Fraumeni syndrome**
  - **Rothmund-Thomson Syndrome** → baseline skeletal abnormalities

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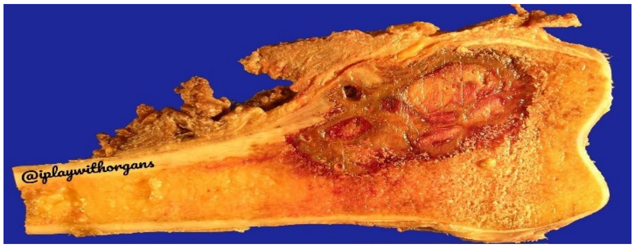
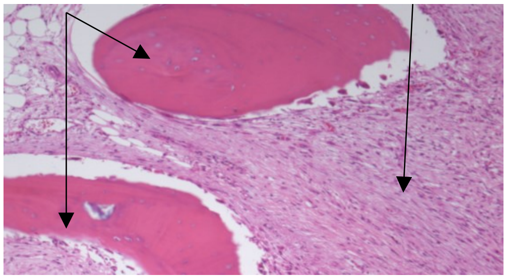
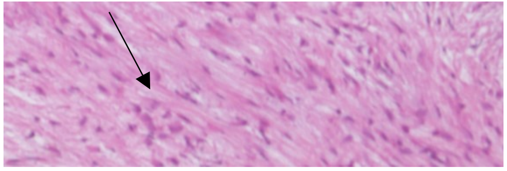


Courtesy of Cory Nash, MS, PA(ASCP) (Twitter: @iplaywithorgans)





Images courtesy of Dr. Bonnie Balzer

LOW-GRADE CENTRAL OSTEOSARCOMA

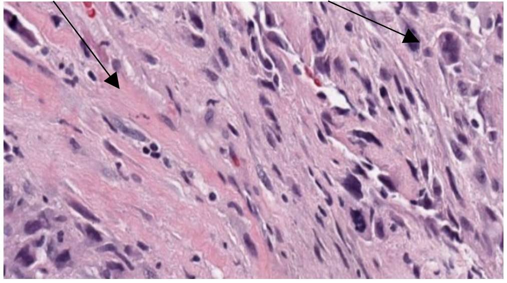
MORPHOLOGY

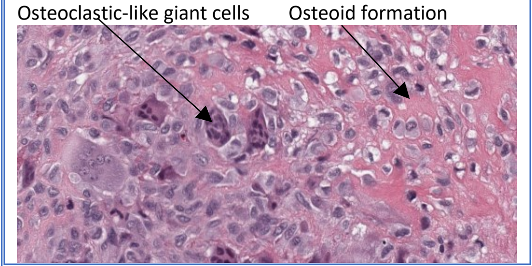
- Moderately **cellular fascicles** of **spindled cells** with only **mild nuclear atypia**
- Admixed (usually woven) **neoplastic bone**, which is composed of **long** and **thick bony trabeculae**, often **in parallel arrangement**

OTHER HIGH YIELD POINTS

- **Very uncommon**, low-grade malignancy (<1% of all osteosarcomas)
- Average age of diagnosis is in **3rd decade,** no sex predilection
- Arises in the **intramedullary cavity** of **long bones** at the **metaphyseal-diaphyseal area** → usually **femur** and **tibia, rare** in **flat bones**
- **Radiology**: **Dense**, **cloud-like** and mineralized lesion, few may be radiolucent
- **Gross examination:** tan-white, gritty, and has cortical destruction
- **Good prognosis** if widely resected but **can dedifferentiate** into conventional osteosarcoma
- **IHC**: Positive for **MDM2** and **CDK4**
- **Molecular**: **MDM2** amplifications

Path Presenter





TELANGIECTATIC OSTEOSARCOMA

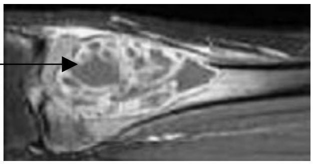
MORPHOLOGY

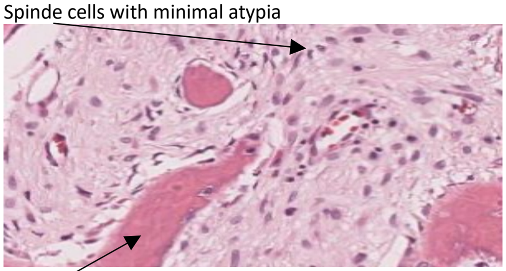
- **Blood-filled** or **empty cystic spaces** separated by variable **fibrous septae**
- **Pleomorphic malignant cells** with significant **nuclear atypia**, **hyperchromasia**, **atypical mitotic figures**, and variable cytoplasm
- Scattered **osteoclast-like giant cells**
- **Focal osteoid formation** and infiltrative border

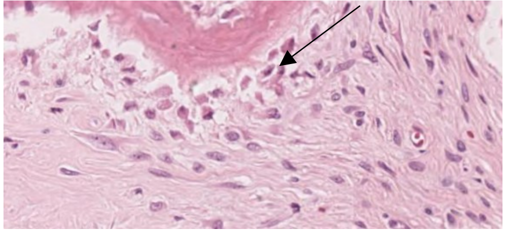
OTHER HIGH YIELD POINTS

- **No prognostic significance** to this subtype of osteosarcoma
- Most common to **arise** in **long tubular bones**
  - **Femur** > **proximal tibia** > proximal humerus
- **Radiology**: Can **present exactly like** an **aneurysmal bone cyst (ABC)**
- Closely **resembles aneurysmal bone cyst** (ABC)
- **Molecular**: Identical to conventional

Path Presenter


Tibia with cystic, blood-filled spaces





Images courtesy of Dr. Bonnie Balzer

PAROSTEAL OSTEOSARCOMA

MORPHOLOGY

- **Spindle cells** with **minimal atypia** and **mitotic** activity
- **Woven bone trabeculae** are long, well-formed, **arranged in parallel**, and have **cement lines** that are **well-visualized**
- Bone may have **osteoblastic rimming**
- **Can dedifferentiate** and have high-grade nuclei with coarse chromatin

OTHER HIGH YIELD POINTS

- **Most common surface**-located **osteosarcoma**
- Majority are in **young adult** to **middle-aged** with slight **female** predominance
- Presents as a **slowly enlarging**, **exophytic lobular mass** on **bone surface**
- Usually on **tubular bone surface** and majority **involve metaphysis**
- **Radiology:** Uniformly **radiodense**, **lobulated contour, surface based**
- **Molecular: MDM2 amplifications** (from **supernumerary ring chromosomes**)
- **Excellent prognosis** and has a >**90% survival** at **5 years**

Path Presenter

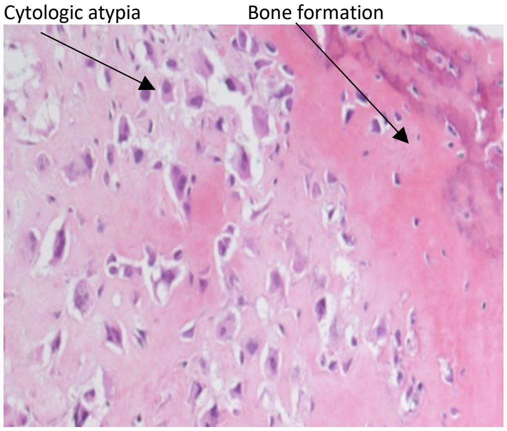


Image courtesy of Dr. Bonnie Balzer

PERIOSTEAL OSTESARCOMA

MORPHOLOGY

- Predominantly a **myxo-hyaline chondroblastic** proliferation
- **Malignant cells** have **moderate to severe** cytologic **atypia** composed of **hyperchromatic nuclei, irregular nuclear contours,** variable cytoplasm
- Intervening **bands** of **primitive sarcoma show bone formation**

OTHER HIGH YIELD POINTS

- **Uncommon** variant, intermediate-grade osteosarcoma
- Usually seen in **young adults** (2-3rd decade) on **surfaces of long bones**
  - **Diaphysis** of **long bones**, especially **femur** and **tibia**
- Presents as a **slow growing**, **palpable mass** that is **non-mobile**
- **Radiology:** Fusiform mass with "sun-burst" or "hair on end" appearance
- Better prognosis than conventional osteosarcoma (~85%, 5-year)

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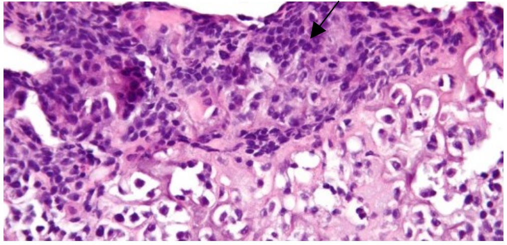
Small cell osteosarcoma Blue cell morphology



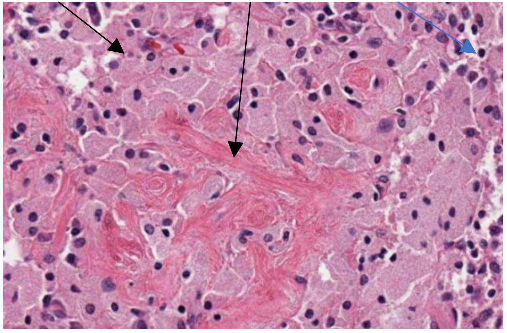
Courtesy of: Dr. Michael Bonert, MD

OTHER OSTEOSARCOMA VARIANTS

MORPHOLOGY

- **Small cell osteosarcoma:** a subtype of conventional osteosarcoma with **small round blue cell** morphology with focal neoplastic bone formation
    - ➢ Tumor cells have **scant cytoplasm** and **fine to coarse chromatin**
    - ➢ Similar distribution to conventional osteosarcoma
- **High-grade surface Osteosarcoma:** histologically high-grade osteosarcoma, but arising on the surface of the bone, without substantial intraosseous involvement

HEMATOPOIETIC NEOPLASMS



ERDHEIM-CHESTER DISEASE

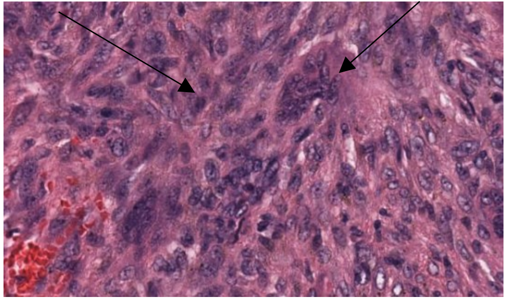
MORPHOLOGY

- Clonal systemic **histiocytosis** with **inflammation** and **fibrosis**
- Infiltration by **foamy**, **lipid-laden histiocytes**
- Variable amounts of mixed inflammatory cells including: **Touton giant cells**, small lymphocytes, neutrophils, and eosinophils
- Fibrosis is usually present and can be extensive

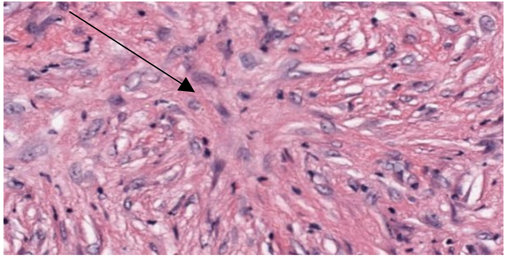
OTHER HIGH YIELD POINTS

- Extremely **rare disease** and arises in **middle-aged to elderly adults**
- Usually involves long bones, but is a multisystem disease
- **IHC**: **Foamy histiocytes** stain with **CD68**, **CD163** and **negative** for **CD1a**
- **Molecular**: BRAFV600E mutations (others: MAPK, ARAF, KRAS, NRAS)

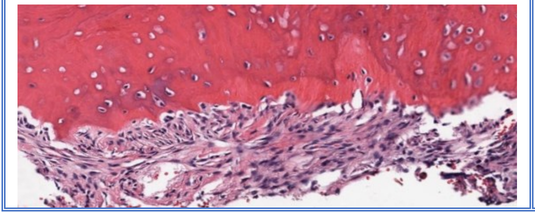
OSTEOCLASTIC GIANT CELL RICH TUMORS



Storiform pattern



Reactive bone



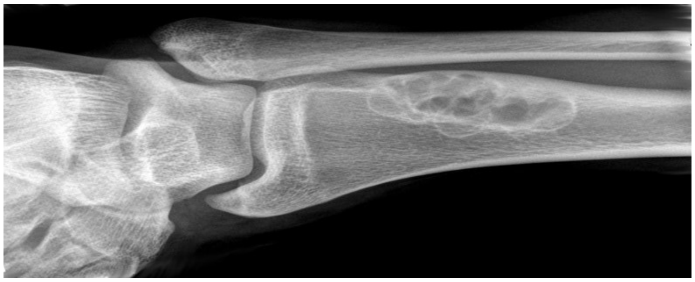
NON-OSSIFYING FIBROMA

MORPHOLOGY

- **Storiform** proliferation of **plump spindled cells** with intermingled **giant cells**
- Scattered **hemosiderophages** and foamy macrophages
- **Necrosis may be present**, especially in a fracture
- Mitotic activity is low
- May have woven bone at the periphery

OTHER HIGH YIELD POINTS

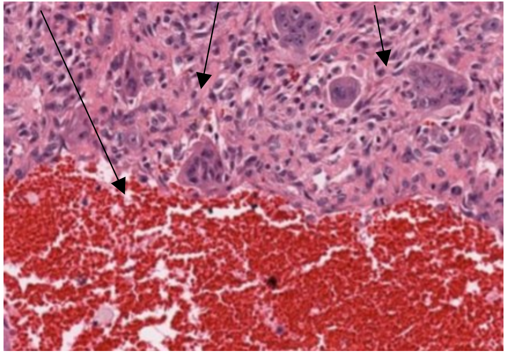
- **Benign asymptomatic lesion** that usually occurs in the **first 2 decades of life**
- **Twice as common in males** than females
- Majority arise in the **metaphysis cortex** of long bones
    - ➢ **Distal femur**, proximal and distal tibia
- **Radiology:** Lucent lesion with sclerotic margin and trabeculations
- **Molecular: KRAS, FGFR1, NF1** mutations → RAS-MAPK pathway activation

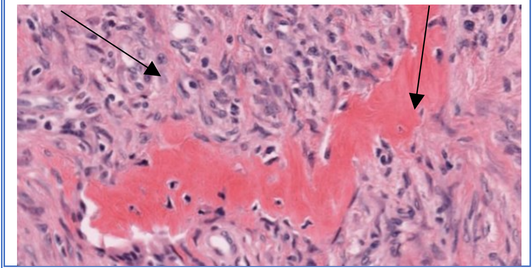


Radiograph courtesy of: Dr. Hellerhoff

Path Presenter

8. BONE AND SOFT TISSUE PATHOLOGY





ANEURYSMAL BONE CYST

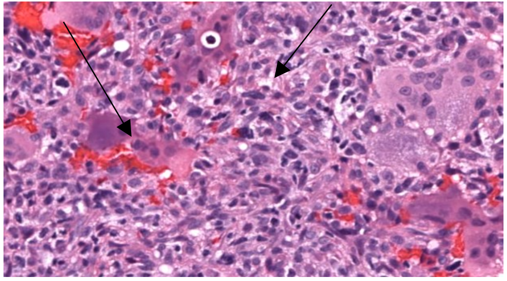
MORPHOLOGY

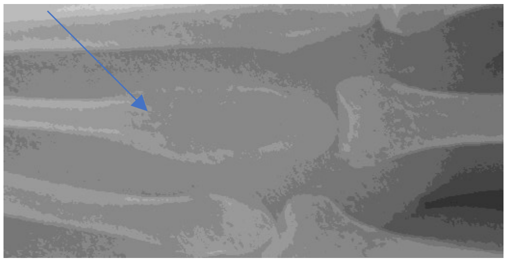
- Cyst wall is composed of **plump** and **spindled fibroblasts**
- **Osteoclast-like giant cells**, **hemorrhage** and hemosiderin
- **Reactive woven bone** formation
- Mitoses are common, necrosis may be present if occurring at site of fracture
- **Solid type lacks blood-filled cystic** spaces

OTHER HIGH YIELD POINTS

- Most **common** in the **first two decades of life**, no sex predilection
- Presents as a **pain** and **swelling** of the affected extremity
- Can arise in the metaphysis of long bones, vertebrae, hands and feet, or craniofacial skeleton
- **Radiology:** Circumscribed, lytic lesion with linear trabeculations and thin sclerotic borders
- **Molecular: CDH11-USP6** translocation → t(16;17)(q22;p13)
- **FISH: USP6 rearrangements**
- Lesions with **secondary ABC:** Giant cell tumor, chondroblastoma, osteoblastoma, fibrous dysplasia, and osteosarcoma

Path Presenter





Radiography courtesy of: Dr. James Heilman, MD

GIANT CELL TUMOR OF BONE

MORPHOLOGY

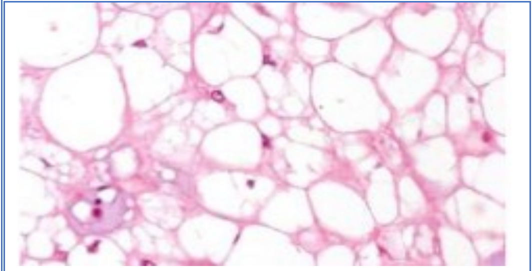
- Proliferation of numerous (reactive) **large osteoclasts** together with a **mononuclear neoplastic** component without atypia
- Mononuclear cells have oval nuclei, regular chromatin and ill-defined cytoplasm and grow in a syncytium
- Often associated with hemorrhage**, hemosiderin,** and macrophages
- Necrosis and vascular invasion can be seen

OTHER HIGH YIELD POINTS

- Usually seen in 3rd to 5th decade with slight female predominance
- Presents as swelling and pain in the affected bone
- Many arise in the **epiphyseal-metaphyseal region** of long tubular bones
    - ➢ Nearly half of cases occur in the knee area
- **Molecular:** Driver mutation in **H3F3A G34W**
- Other giant cell tumor of bone:
    - ➢ Chondroblastoma, Paget's disease of Bone, some osteosarcomas, Non-ossifying fibroma, aneurysmal bone cyst

Path Presenter

NOTOCHORDAL TUMORS



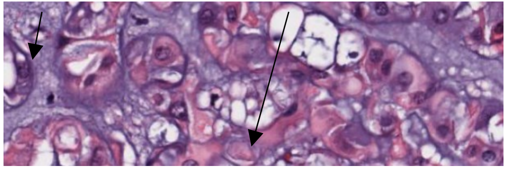
BENIGN NOTOCHORDAL TUMOR

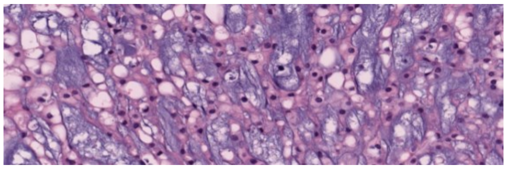
MORPHOLOGY

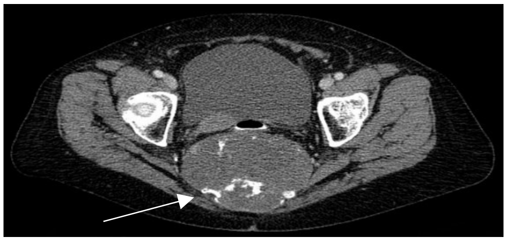
- Polyhedral epithelioid cells with bland nuclei with fine chromatin, abundant clear to eosinophilic cytoplasm, and well-defined cell borders
- No extracellular myxoid matrix, vasculature, fibrous septae, or lobular architecture

OTHER HIGH YIELD POINTS

- Benign and usually in axial skeleton: Sacrum, coccyx, cervical spine, vertebrae
- IHC: Positive for Brachyury, S100, keratin, and EMA




Cords


Chordoma

CT Scan courtesy of Dr. Hellerhoff

CHORDOMA

MORPHOLOGY

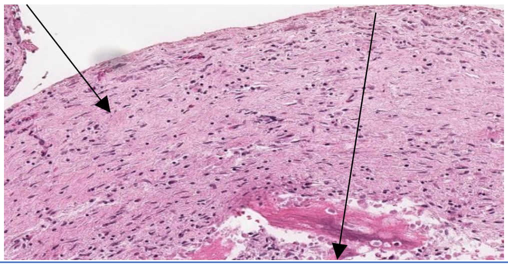
- **Large epithelioid cells** with eosinophilic to clear cytoplasm and may have bubbly **"physaliphorous"** cytoplasm
- Arranged in **cords** and **nests** embedded in **abundant myxoid matrix** or separated by **fibrous septae**
- **Variable pleomorphism** and mitotic activity

OTHER HIGH YIELD POINTS

- Usually seen in middle-aged to elderly patients with male predilection
  - If arising in **children**, usually is at **skull base**
- Presentation dependent on site of origin
  - **Skull base:** diplopia, headache, cranial nerve palsy
  - **Spine:** neurologic symptoms and pain
  - **Sacrum:** pain, incontinence, constipation, erectile dysfunction
- **Radiology**: destructive lytic mass and variable calcifications
- Prognosis: Depends on size, location, and dedifferentiation (poor)
- IHC: Positive for **brachyury**, **cytokeratin 8/19**
- Molecular: **T-box duplication (Brachyury),** PI3K pathway, LYST, others
  - **Poorly differentiated chordoma**: loss of **SMARCB1**, and has scattered signet ring-like cells and rhabdoid areas

Path Presenter

MISCELLANOUS BONE LESIONS



SIMPLE BONE CYST

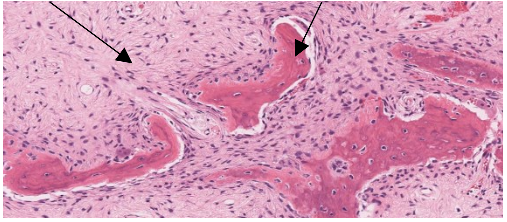
MORPHOLOGY

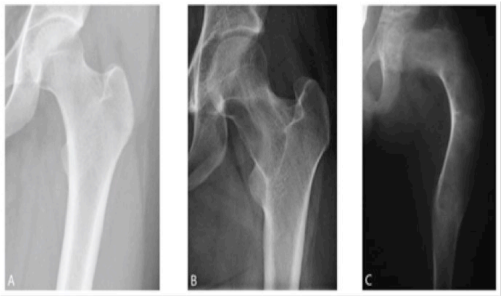
- Cyst wall composed of **fibrous tissue** with **no true lining**
- May have reactive woven bone formation, chronic inflammation, multinucleated giant cells, fibrin, calcification, and cholesterol

OTHER HIGH YIELD POINTS

- Benign lesion seen in the proximal femur or humerus of young patient

Path Presenter




Normal Fibrous Dysplasia Shepherd's Crook

Radiography courtesy of Dr. Basmajoor

FIBROUS DYSPLASIA

MORPHOLOGY

- Fibrous tissue composed of **spindled cells** with **tapered nuclei** and **inconspicuous** cytoplasmic **borders**
- Bone trabeculae are composed of **curvilinear woven bone** and appear to "arise" from the fibrous tissue

OTHER HIGH YIELD POINTS

- Most commonly develops during childhood and may be associated with genetic syndromes
  - **Mazabraud syndrome:** Fibrous dysplasia and intramuscular myxomas
  - **McCune-Albright syndrome:** Fibrous dysplasia, café-au-lait macules, and endocrinopathies
- **Radiology**: Elongated intramedullary tumor with "rind-like" margins; severe cases have "**shepherd's crook**" appearance
- May be **monostotic** or **polyostotic** and involve many different sites
- Most **common extraskeletal manifestation** is "**café-au-lait**" macules
- **Molecular:** Activating **GNAS** missense mutations in polyostotic form

Path Presenter

8. BONE AND SOFT TISSUE PATHOLOGY

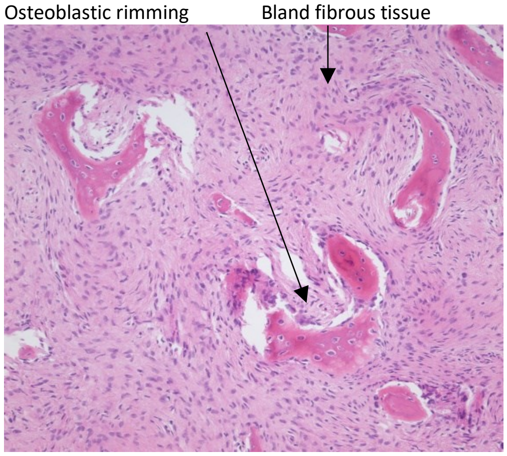


Image courtesy of Dr. Bonnie Balzer

OSTEOFIBROUS DYSPLASIA

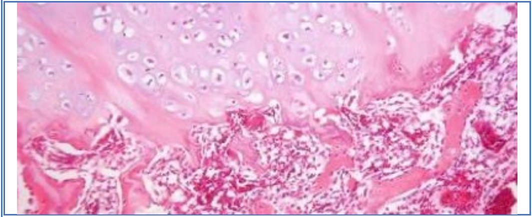
MORPHOLOGY

- Woven bone with prominent **osteoblastic rimming** with intervening bland fibrous tissue

OTHER HIGH YIELD POINTS

- Benign lesion occurring in the first 2 decades of life
- Almost exclusively in **tibia or fibula anterior cortex** during childhood
- Presents as a pain, localized swelling, or fracture
- Radiology: Solitary lytic lesion with sclerotic borders
- IHC: **Positive** for **cytokeratin** which highlights scattered **single cells**
  - **If CK highlights clusters of cells, consider:** Osteofibrous dysplasia-like adamantinoma
- **Molecular:** Germline MET mutations (hereditary OFD); lacks GNAS mutations

Path Presenter



CHONDROMESENCYMAL HAMARTOMA OF CHEST WALL

MORPHOLOGY

- Composed of **nodules of hyaline cartilage**, admixed with blood-filled cystic spaces, reactive bone, bland spindled cells, and osteoclast-like giant cells

OTHER HIGH YIELD POINTS

- Benign
- Well-circumscribed mass arising from the rib, **presents at birth**

NON-NEOPLASTIC SEROSAL LESIONS

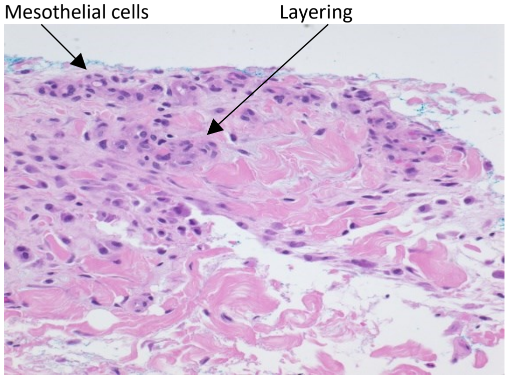


Image courtesy of Dr. Bonnie Balzer

REACTIVE MESOTHELIAL HYPERPLASIA

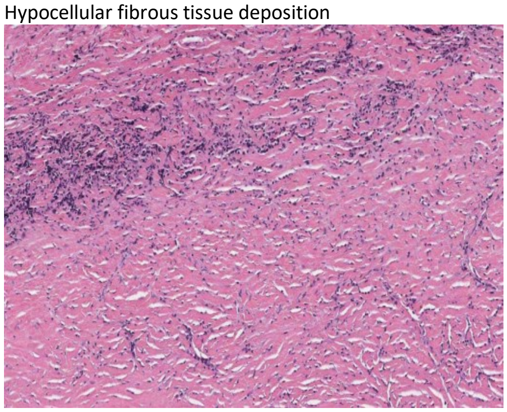
MORPHOLOGY

- Thickened pleura containing sheets or clusters of mesothelial cells
- May have papillary excrescences
- Can have psammomatous calcifications
- May demonstrate layering of fibrous tissue and mesothelium
  - "Sedimentary-rock appearance"

OTHER HIGH YIELD POINTS

- Seen with recurrent pleural irritation, resolves when stimulus removed
- IHC: **Positive** for **calretinin**, **WT-1**, D2-40, CK5/6 and **retained BAP1** expression

Path Presenter



FIBROUS PLEURISY

MORPHOLOGY

- Deposition of **bland**, **hypocellular fibrous tissue** in the pleura
- Often involves the visceral pleura
- May produce **apical fibrous** "**capping**"

OTHER HIGH YIELD POINTS

- Often involves the **visceral pleura** and may produce apical fibrous "capping"
- Severe cases can obliterate the pleural space
- Can **mimic desmoplastic mesothelioma**
- May be **associated with a variety of conditions**
  - **Connective tissue disorders:** lupus erythematosus or rheumatoid arthritis
  - **Chronic infections**
  - **Asbestos exposure**

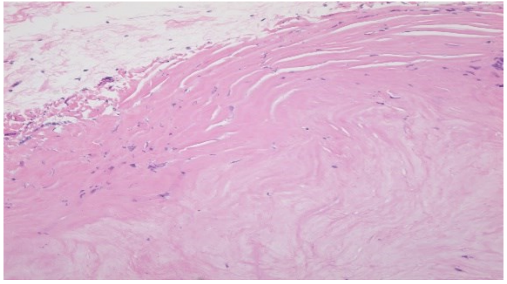

Dense hyalinized collagen

Image courtesy of Dr. Bonnie Balzer

PLEURAL PLAQUE (HYALINE PLEURAL PLAQUE)

MORPHOLOGY

- **Hypocellular**, **dense bundles** of **hyalinized collagen**, often with a “basket weave” arrangement
- Often dystrophic calcifications and variable chronic inflammation

OTHER HIGH YIELD POINTS

- Often on parietal pleura, particularly on diaphragm
- Often a **marker of asbestos exposure**, but **can be seen with other sources** of chronic pleural irritation

Path Presenter

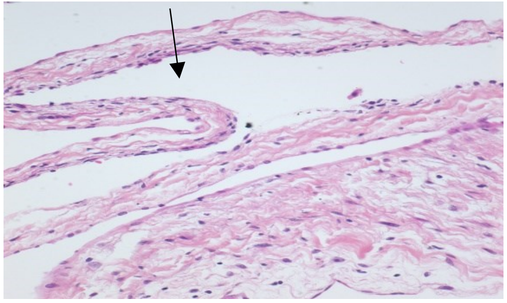

Single layer, benign mesothelial cells

Image courtesy of Dr. Bonnie Balzer

PERITONEAL INCLUSION CYST

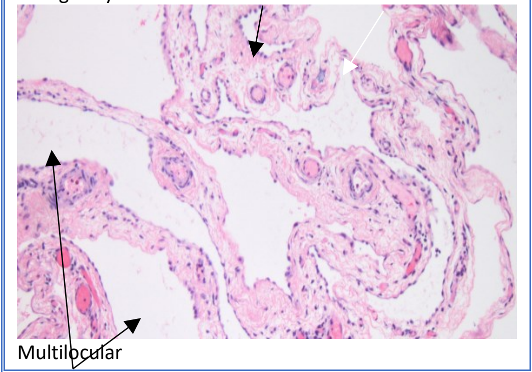
MORPHOLOGY

- Single or multiple, **small, thin-walled, translucent, unilocular cysts**
- Attached or free in the peritoneal cavity
- Lined by a **single layer** of flattened, benign-appearing mesothelial cells
- Variable thickened septae within the cyst and

OTHER HIGH YIELD POINTS

- Often discovered incidentally, more **common in women**
  - **Common** in **pelvic organs, upper abdominal cavity,** or **retroperitoneum**

Path Presenter


A single layer of flattened hobnailed mesothelial cells

Multilocular

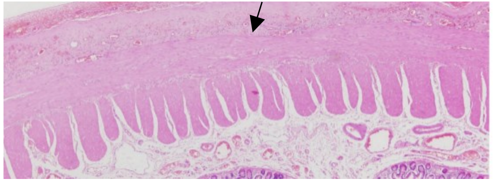
BENIGN MULTICYSTIC PERITONEAL “MESOTHELIOMA”

MORPHOLOGY

- Grossly: often **large**, **multiple small**, **thin-walled**, **translucent**, unilocular **cysts** that may be attached or free floating
- Often fibrous tissue in septae with sparse inflammation
- Cysts are lined by a single layer of flattened to cuboidal mesothelial cells which occasionally have a “**hob-nail**” appearance

OTHER HIGH YIELD POINTS

- Occurs usually in **young to middle-aged women** in the **peritoneum or pelvis**
- Better name is “**multilocular peritoneal inclusion cysts**”
- Likely a hyperplastic reactive lesion (vs. a benign neoplasm)
- **Associated** with **previous abdominal surgery**, **pelvic inflammatory disease**, and **endometriosis**


Bowel encapsulated by fibrous tissue

Courtesy: Dr. I Ruz-Caracuel

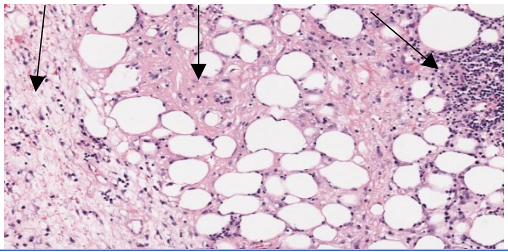
SCLEROSING PERITONITIS

MORPHOLOGY

- Encasement of the bowel by fibrous tissue

OTHER HIGH YIELD POINTS

- Rare, causes bowel obstruction from encasement →“Cacoon abdomen”
- Can be idiopathic, or seen with intraperitoneal dialysis, VP shunts, and fibrothecomas of the ovary


Fibrosis Fat necrosis Inflammation

SCLEROSISING MESENTERITIS

MORPHOLOGY

- Varying degrees of fat necrosis, chronic inflammation, and fibrosis, usually involving the mesentery of the small bowel → forms a **distinct mass**

OTHER HIGH YIELD POINTS

- Rare, idiopathic, forms a distinct mass involving the small bowel mesentery

Path Presenter

BENIGN/INDOLENT MESOTHELIAL TUMORS

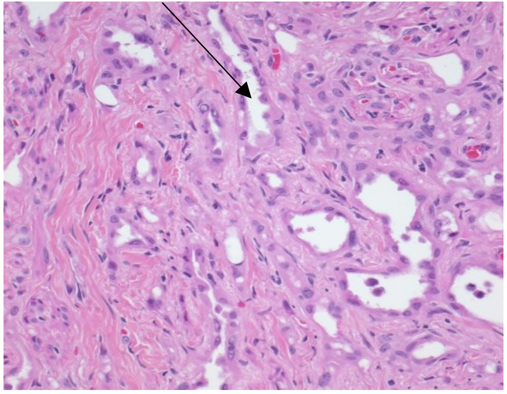


Image courtesy of Dr. Bonnie Balzer

ADENOMATOID TUMOR

MORPHOLOGY

- **Irregularly shaped gland-like microcystic spaces** composed of flattened or cuboidal cells with associated fibrous stroma
- **Bland cytologic features**
- Helpful feature: "thread-like bridging strands"; Sometimes signet ring-like vacuolated cells

OTHER HIGH YIELD POINTS

- Solitary, localized lesion that occurs in both **males** and **females**
- Seen in young to middle-aged adults
- May be seen in **uterine** or **adnexal surfaces**, **testis**, or **spermatic cord**
- Presents as a firm painless mass

Path Presenter

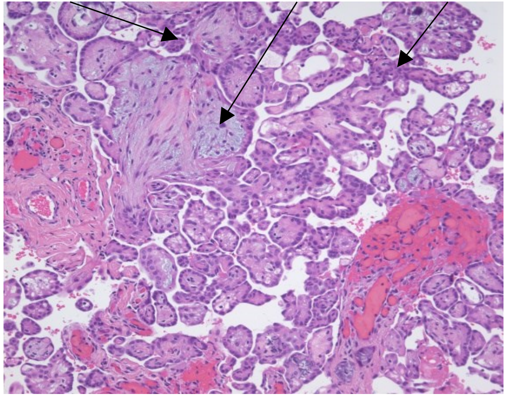


Image courtesy of Dr. Bonnie Balzer

WELL DIFFERENTIATED PAPILLARY MESOTHELIOMA

MORPHOLOGY

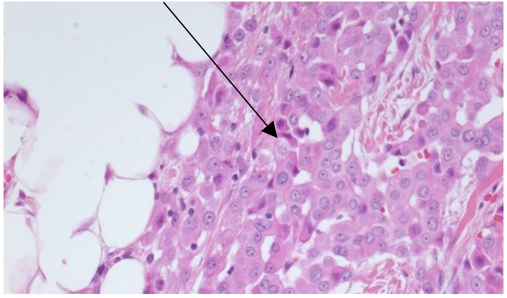
- **Prominent papillary architecture** with myxoid cores covered by a single layer of **flattened to cuboidal bland epithelioid cells**
- Epithelioid cells have small bland round **nuclei**, **without atypia**
- No inflammatory reaction is present

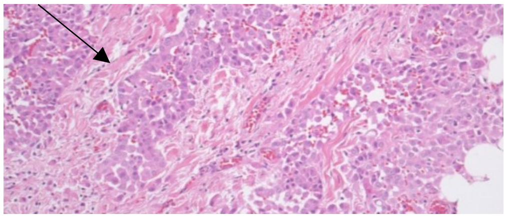
OTHER HIGH YIELD POINTS

- Rare indolent tumors, most cases cured by excision
- Average survival is ~75 months
- Gross examination: velvety appearance
- **IHC**: Positive for pancytokeratin, CK5/6, calretinin, D2-40, WT1, GLUT1
- **Molecular:** Somatic missense mutations in **TRAF7** or **CDC42**

Path Presenter

MALIGNANT MESOTHELIAL TUMORS





Images courtesy of Dr. Bonnie Balzer

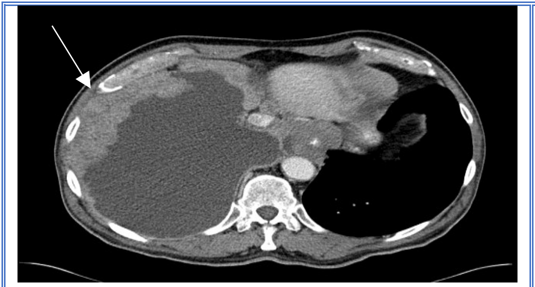
EPITHELIOID MESOTHELIOMA

MORPHOLOGY

- **Malignant** proliferation of mesothelial cells with **epithelioid morphology**
- Cytologically bland with **eosinophilic cytoplasm** and **vesicular chromatin**
- Demonstration of tissue invasion (e.g., into chest wall or lung) is often key for diagnosis
  - However, when a substantial amount of solid, malignant tumor (i.e., a mass) is identified, the presence of invasion is not required for diagnosis
- **Common histologic patterns**: solid, tubulopapillary, trabecular
- **Rare patterns**: micropapillary, clear cell, deciduoid, adenomatoid, transitional, small cell, lymphohistiocytoid
- Can see psamomma bodies

OTHER HIGH YIELD POINTS

- Most common in **elderly males** and often **unilateral** at first
- Most common cause is **asbestos exposure**
- Often **insidious onset** with **chest pain** and/or **dyspnea**
- Prognosis depends on extent of involvment
  - Usually **diffuse** (**circumferential**, rind-like) → **Poor** prognosis
  - Rarely, **localized** (**solitary**, well-circumscribed) → **Better** prognosis

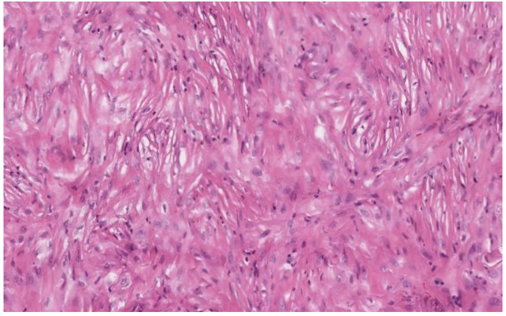


CT Scan courtesy of Dr. Thomas Dvorak, MD

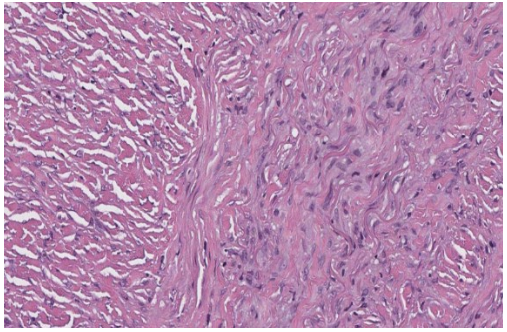
- Clinical information (either from imaging or intraoperative findings) can be very helpful with diagnosis:
  - **Circumferential** pleural **thickening** is **highly suggestive** of **malignancy**
  - **Nodular pleural thickening** is also often **malignant**
- **IHC**: Positive for mesothelial markers, l**oss of BAP1** or **MTAP** expression
- **FISH**: **CDKN2A** (p16) **deletion**
- **Molecular:** Often multiple chromosomal alterations
  - Frequent loss of tumor suppressors CDKN2A, BAP1, and NF2

Path Presenter

Haphazard spindle cells (sarcomatoid mesothelioma)



Infiltrating malignant cells in desmoplastic stroma



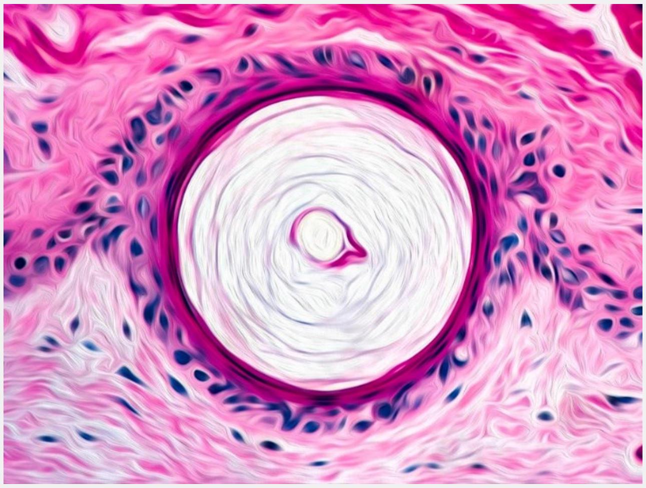
SARCOMATOID, DESMOPLASTIC, AND BIPHASIC MESOTHELIOMA

MORPHOLOGY

- **Sarcomatoid mesothelioma**:
  - **Spindle cell** appearance
  - Arranged in **fascicles** or **haphazardly**
  - Can see **heterologous elements** (e.g., rhabdomyosarcoma)
- **Desmoplastic mesothelioma**:
  - **Dense collagenized tissue** with malignant mesothelial cells
  - Either **patternless** or **storiform** pattern
  - Must be **≥50% of tumor**
  - **Invasion** into fat is most helpful feature to differentiate from organizing pleuritis
- **Biphasic mesothelioma**:
  - Contains BOTH epithelioid and sarcomatoid patterns, **each ≥10%**
  - Stromal invasion is often more difficult to recognize in these spindle cell proliferations as the invasive malignant cells are often deceptively bland → Use IHC liberally

OTHER HIGH YIELD POINTS

- Poorer prognosis than epithelioid mesotheliomas
  - **Desmoplastic mesothelioma** has a **particularly dismal prognosis** (often less than 6 months)
- **IHC**: Usually stain (at least focally) with a broad spectrum pancytokeratin (can also help to demonstrate invasion)
  - **Loss of BAP1** is **very uncommon** in these types

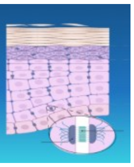


Skin appendage, H&E stain. Microscopic picture with digital filter applied for artistic effect, appearing as an "eye". Image courtesy: Ziad El-Zaatari, MD

CHAPTER 9: SKIN PATHOLOGY

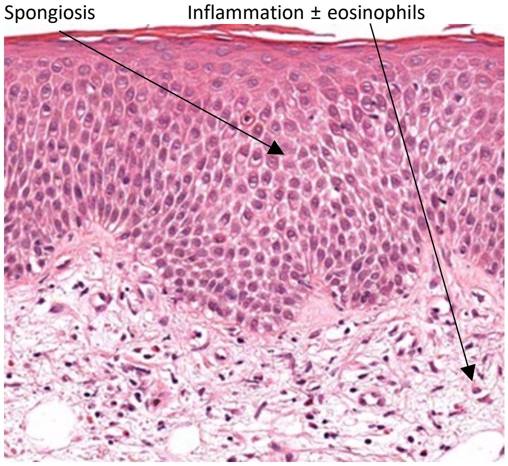
Dinesh Pradhan, MD
Naomi Hardy, MD
Amandeep Kaur, MD
Akanksha Gupta, MD

9. SKIN PATHOLOGY



NONNEOPLASTIC DERMATOPATHOLOGY

SPONGIOTIC DERMATOSES


Spongiosis
Inflammation ± eosinophils

SPONGIOTIC DERMATITIS

MORPHOLOGY

- Intraepidermal intercellular edema (**spongiosis**)
- Presence of widened intercellular spaces between keratinocytes, with elongation of the intercellular bridges
- Superficial dermal inflammation ± **eosinophils** can be seen
- Acute (microvesicles), Chronic (acanthosis, psoriasiform hyperplasia, lichenification)

OTHER HIGH YIELD POINTS: ATOPIC DERMATITIS

- Clinically intensely pruritic, vesicles, papules and plaques
- Aka **eczema or eczematous dermatitis**
- Histologically similar: atopic, contact, nummular dermatitis and Id reaction
- **Atopic Triad:** 1) Atopic dermatitis, 2) Seasonal allergies, 3) Asthma

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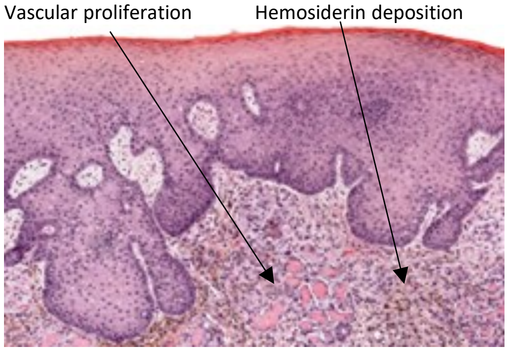
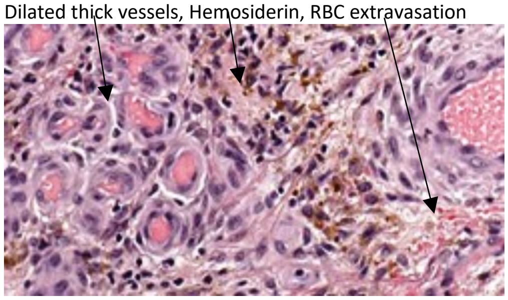

Vascular proliferation
Hemosiderin deposition


Dilated thick vessels, Hemosiderin, RBC extravasation

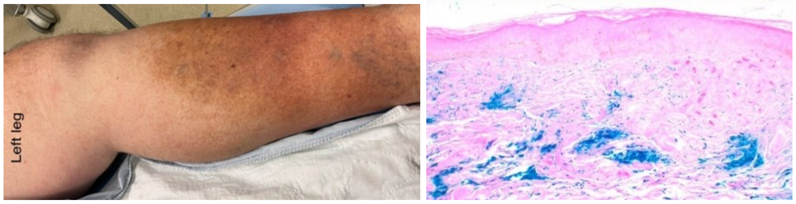
STASIS DERMATITIS

MORPHOLOGY

- Spongiotic dermatitis
- **Vascular proliferation,** dilated, thickened blood vessels in papillary dermis
- RBCs extravasation, **hemosiderin** deposition
- Can have chronic inflammation

OTHER HIGH YIELD POINTS

- Begins on **medial aspect on lower legs** but can become circumferential
- Clinically **mimics cellulitis**
- Prussian blue (iron stain) positive



Medial aspect of lower leg; Prussian Blue stain, Credit: Jose Candido, MD

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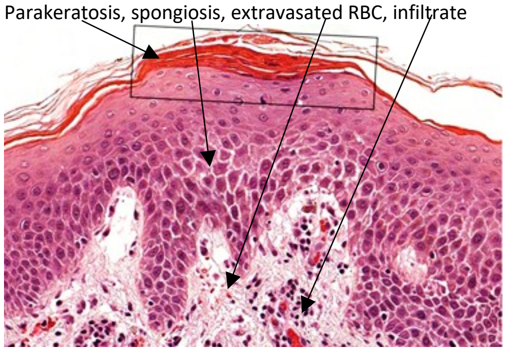

Parakeratosis, spongiosis, extravasated RBC, infiltrate

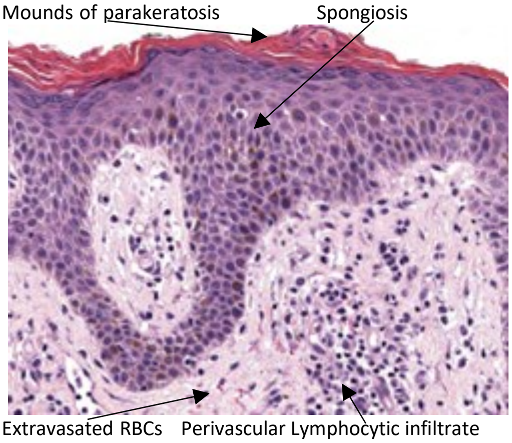
PITYRIASIS ROSEA

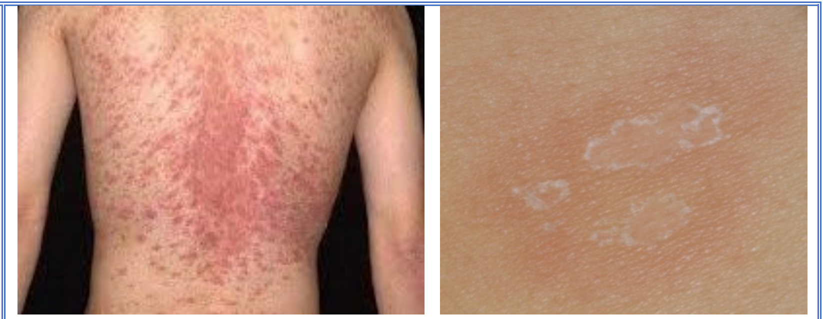
MORPHOLOGY

- Spongiotic dermatitis
- **Mounds of parakeratosis**
- Extravasated RBC.
- Superficial perivascular lymphohistiocytic infiltrate

OTHER HIGH YIELD POINTS

- Flu-like prodrome 2-3 weeks before eruption
- Clinically starts with **Herald patch** (salmon-colored plaque)
- The Herald patch increases in size over 48 hours.
- Eventually a **Christmas tree pattern** develops


Mounds of parakeratosis
Spongiosis
Extravasated RBCs
Perivascular Lymphocytic infiltrate



Herald’s Patch and Christmas tree pattern, collarette scaling at the periphery of the lesion

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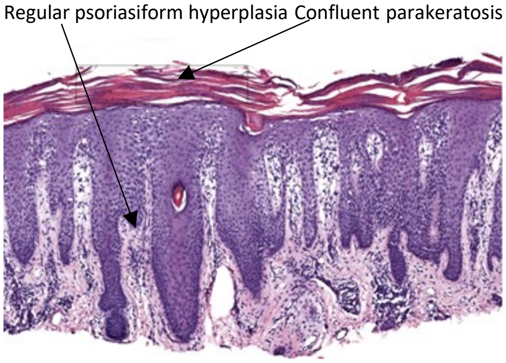
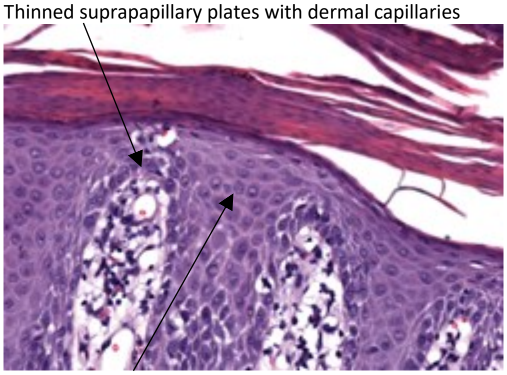
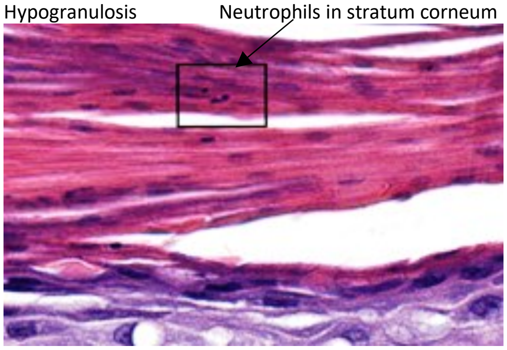
PSORIASIFORM DERMATOSES


Regular psoriasiform hyperplasia
Confluent parakeratosis


Thinned suprapapillary plates with dermal capillaries


Hypogranulosis
Neutrophils in stratum corneum

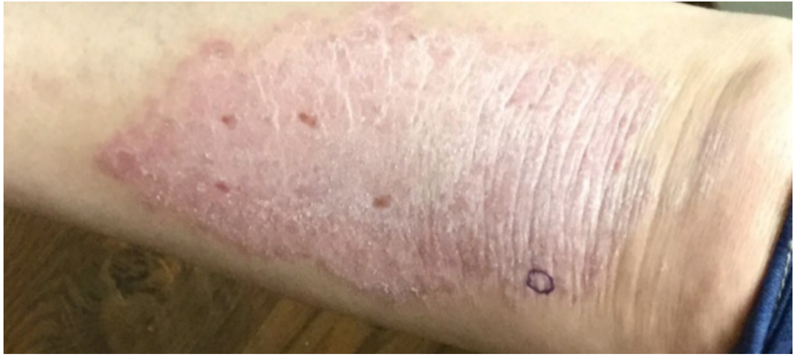
PSORIASIS

MORPHOLOGY

- Regular **psoriasiform hyperplasia**
- **Confluent parakeratosis**
- Hypogranulosis
- Neutrophils in the stratum corneum/epidermis
- Suprapapillary plates are **thinned** beneath which are **dilated tortuous capillaries** within the dermal papillae

OTHER HIGH YIELD POINTS

- Clinically erythematous plaques and **silvery white scale**
- Mostly on **extensor** surfaces
- **Auspitz sign**: Pinpoint bleeding when scale is removed
- **Munro microabscess**: Neutrophil collection in corneal layer
- **Spongiform pustules of Kogoj**: Neutrophil collection in spinous layer
- Variants: Guttate, pustular, inverse, nail and erythrodermic psoriasis
- **Reiter Syndrome**: Conjunctivitis, Urethritis, Arthritis with psoriasiform skin lesions
- **Erythroderma - SCALP-ID** - Sezary syndrome, Contact dermatitis, Atopic dermatitis, Lymphoma/Leukemia, Psoriasis, Idiopathic, Drug



Silvery white scale

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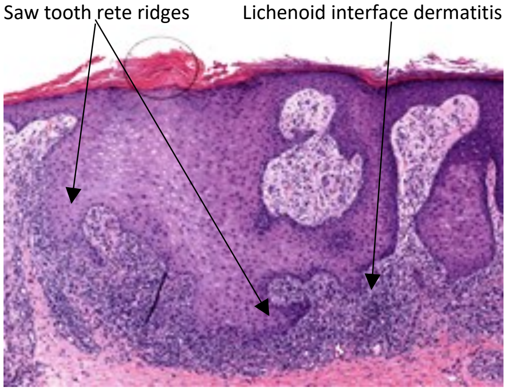
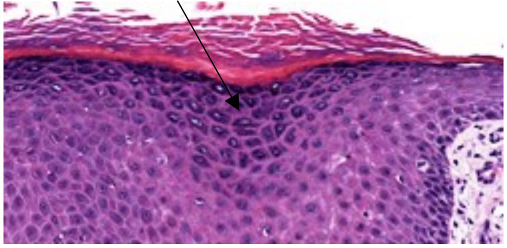
LICHENOID AND INTERFACE DERMATOSES

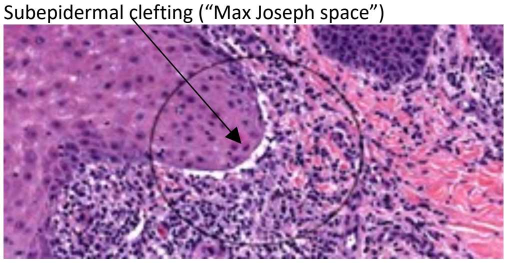


Saw tooth rete ridges

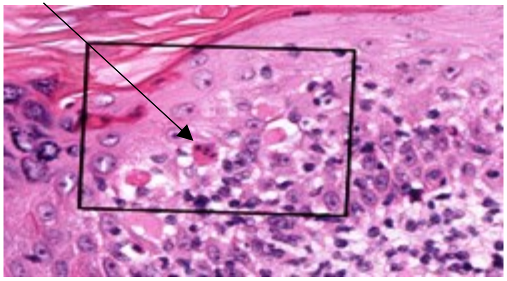
Lichenoid interface dermatitis



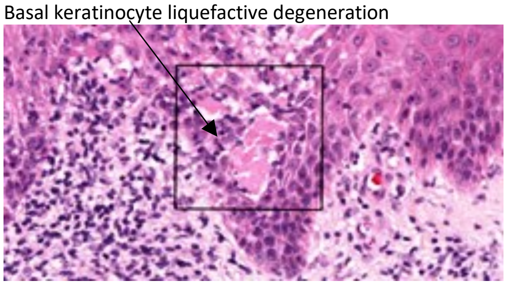
Wedge-shaped hypergranulosis



Subepidermal clefting (“Max Joseph space”)



Civatte bodies



Basal keratinocyte liquefactive degeneration

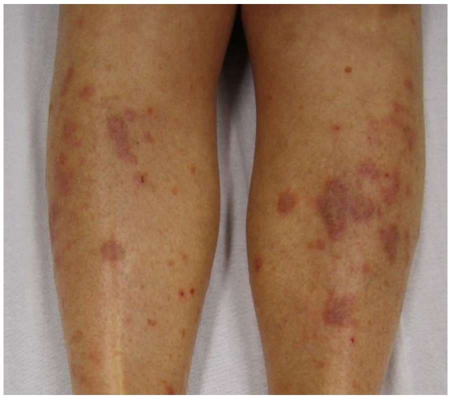
LICHEN PLANUS

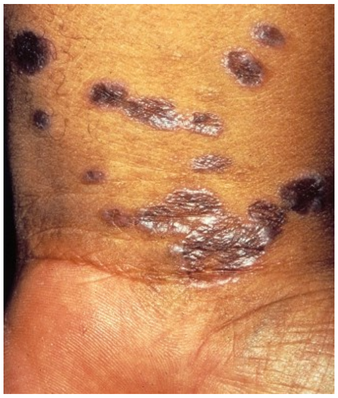
MORPHOLOGY

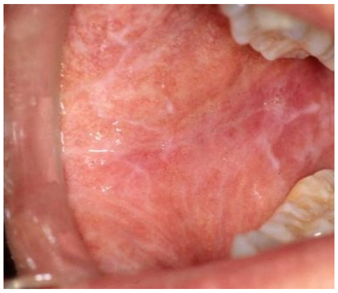
- **Lichenoid interface dermatitis** - Band-like inflammatory Infiltrate at dermoepidermal junction
- Compact hyperkeratosis without parakeratosis, compact hyperorthokeratosis
- Wedge-shaped hypergranulosis
- “**Saw-tooth**” rete ridges
- Basal keratinocyte liquefactive degeneration
- Subepidermal clefting (“Max Joseph space”)
- **Civatte bodies** and **Colloid bodies** (necrotic keratinocytes in epidermis and dermis, respectively)

OTHER HIGH YIELD POINTS

- Clinically pruritic, purple, planar, and polygonal papules (5Ps)
- Distribution over flexural wrists, ankles, arms, legs, trunks, genitalia, and oral mucosa. The face is rarely affected
- Wickham striae: reticulate network of lacy white scaling
- Main differential - Benign Lichenoid Keratosis (single lesion on trunk)
- Direct immunofluorescence (DIF) - Predominantly IgM and fibrin staining of colloid bodies







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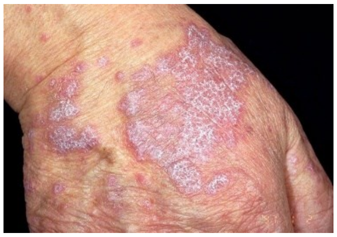
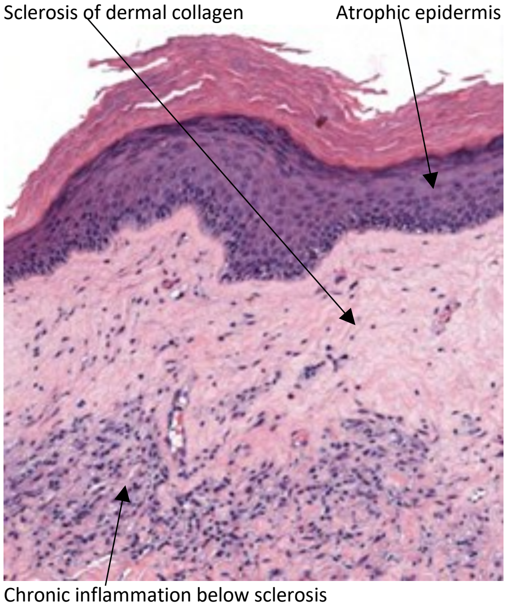



Sclerosis of dermal collagen
Atrophic epidermis
Chronic inflammation below sclerosis

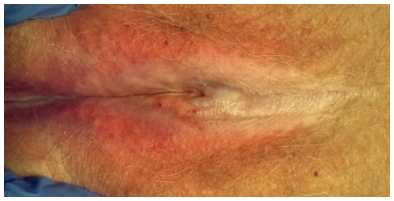
LICHEN SCLEROSUS ET ATROPHICUS

MORPHOLOGY

- Homogenization/ **sclerosis of dermal collagen**
- Chronic inflammation below edema and homogenization
- Atrophic epidermis
- Early lesions - lichenoid interface dermatitis

OTHER HIGH YIELD POINTS

- Aka lichen sclerosus or **balanitis xerotica** obliterans (glans penis)
- Predilection for anogenital skin
- Clinically ivory white plaques with **cigarette paper**-like appearance



Courtesy: Mikael Häggström, MD

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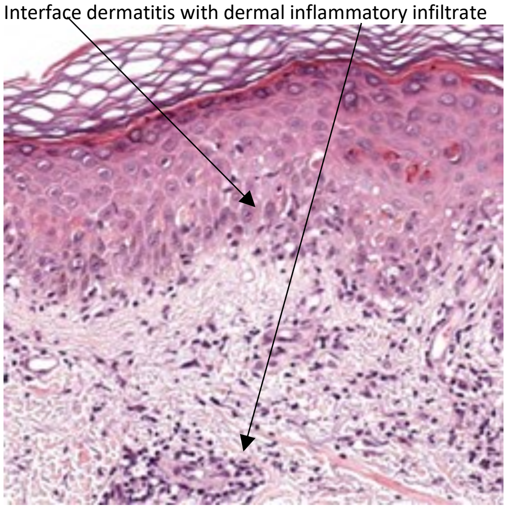
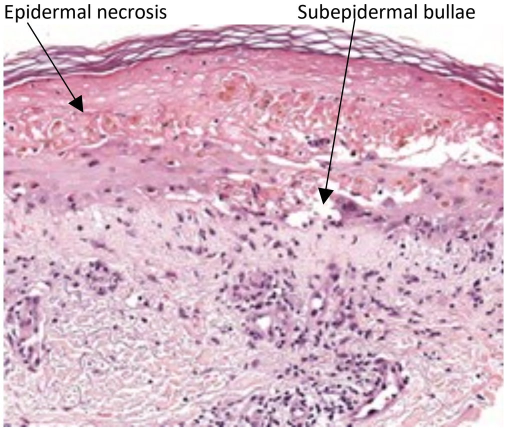

Interface dermatitis with dermal inflammatory infiltrate


Epidermal necrosis
Subepidermal bullae

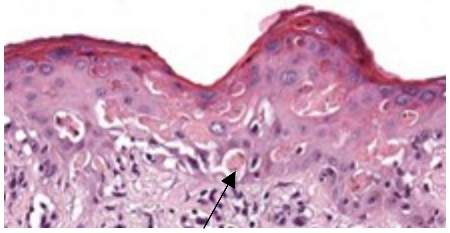
ERYTHEMA MULTIFORME

MORPHOLOGY

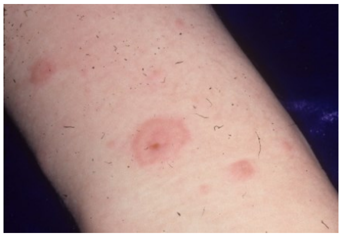
- **Erythema multiforme (EM) - Interface dermatitis** with necrotic keratinocytes
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) - **Full-thickness epidermal necrosis**
- **Subepidermal bullae** with basement membrane in bullae roof due to dermal edema
- Severe **dermal perivascular inflammatory infiltrate** (lymphocytes)
- Eosinophils may be present, but neutrophils are sparse or absent
- Overlying epidermis often demonstrates **liquefactive necrosis** and degeneration, **dyskeratotic keratinocytes**
- May also have dermoepidermal bullae with basal lamina at floor of bullae
- No leukocytoclasis, no microabscesses, no festooning of dermal papillae

OTHER HIGH YIELD POINTS

- On spectrum with SJS/TEN
- Reactive in nature (mainly due to **HSV, Mycoplasma, or Drug**)
- SJS/TEN - Serious, life-threatening reaction
- EM - Acute, self-limited disease
- Clinically, targetoid dusky lesions on acral sites and face



Dyskeratotic keratinocytes



Targetoid dusky lesion

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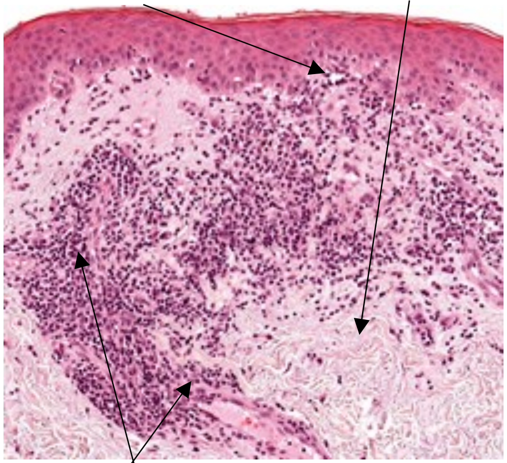
CONNECTIVE TISSUE/SOFT TISSUE DISEASES


Vacuolar interface dermatitis
Increased dermal mucin
Superficial & deep perivascular & periadnexal infiltrate

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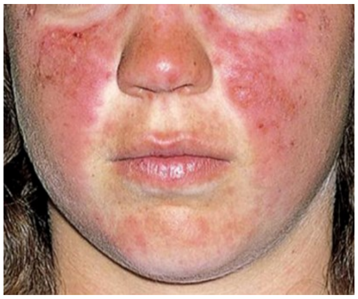
LUPUS ERYTHEMATOSUS (LE)

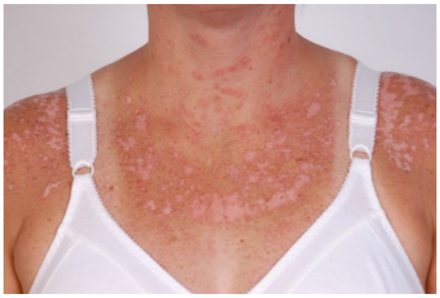
MORPHOLOGY

- **Vacuolar interface dermatitis** with dyskeratotic keratinocytes
- Thickened basement membrane
- **Superficial and deep** perivascular and periadnexal lymphohistiocytic infiltrate
- Increased **dermal mucin**

OTHER HIGH YIELD POINTS

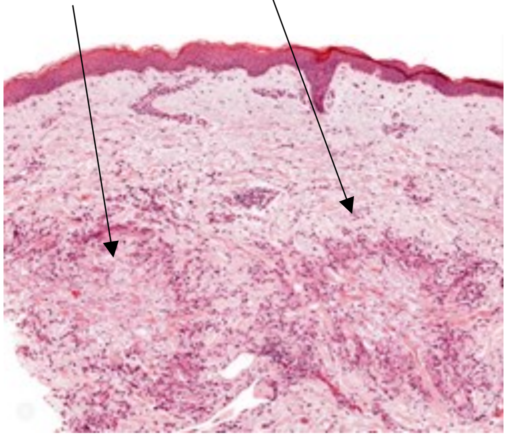
- Acute and subacute cutaneous LE: Associated with systemic diseases
- Chronic cutaneous LE /discoid LE (DLE)- usually only limited to the skin
- Immunofluorescence: IgM, IgG, C3 - granular BM deposition
- Tumid LE - No interface dermatitis



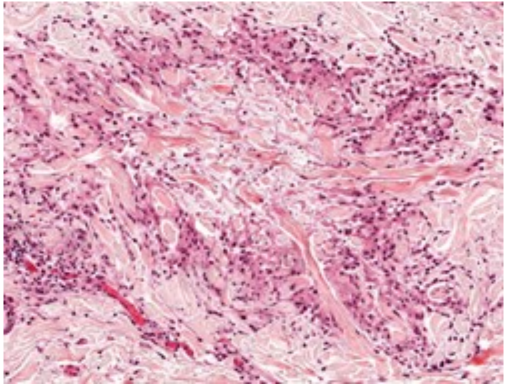


GRANULOMATOUS DISEASES

Central mucin with palisaded histiocytes



Classic granuloma annulare



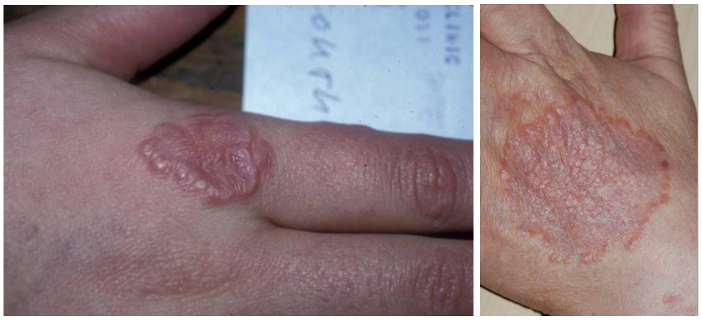
GRANULOMA ANNULARE (GA)

MORPHOLOGY

- **Central mucin** with surrounding palisaded histiocytes
- Mucin can be stained with **Alcian blue** or **colloidal iron**
- Histologic variants include classic (or palisading) GA, interstitial GA, deep (or subcutaneous) GA, and perforating GA
- Deep GA - in subcutaneous tissues
- Interstitial pattern - Interstitial histiocytes

OTHER HIGH YIELD POINTS

- Clinically rashes are often **annular** (round) or arcuate non-scaly red-brown plaques with **central clearing**
- Most commonly on **arms/legs** or **back of hands/feet**
- **Self-limited** dermatoses
- Unknown etiology



Annular / arcuate red brown plaque

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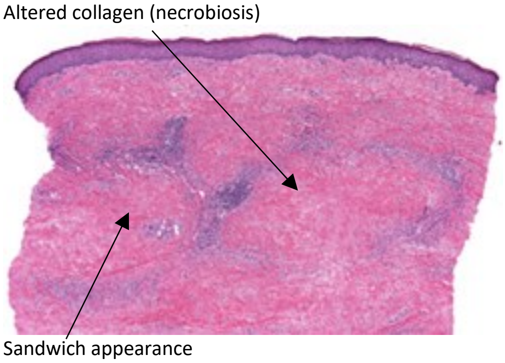
9. SKIN PATHOLOGY


Altered collagen (necrobiosis)
Sandwich appearance

NECROBIOSIS LIPOIDICA

MORPHOLOGY

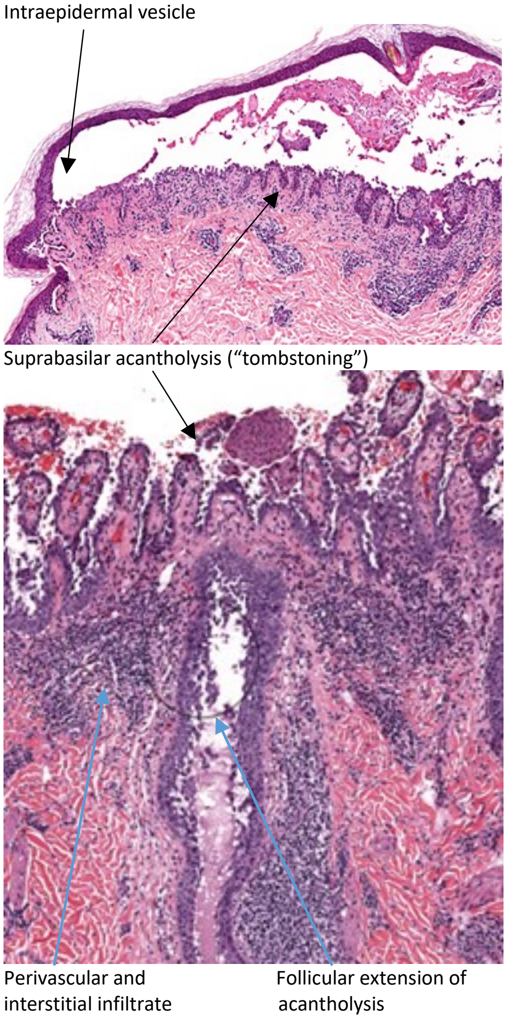
- **Layers of altered collagen (necrobiosis)** alternating with layers of inflammation (**sandwich appearance**)
- Epithelioid granulomas or cholesterol clefts may be seen

OTHER HIGH YIELD POINTS

- Often involves **bilateral shins**
- Differential diagnosis - Granuloma Annulare, Rheumatoid nodule
- Associated with diabetes - aka Necrobiosis lipoidica diabeticorum (NLD)

Path Presenter

VESICULOBULLOUS DERMATOSES


Intraepidermal vesicle
Suprabasilar acantholysis ("tombstoning")
Perivascular and interstitial infiltrate
Follicular extension of acantholysis

Path Presenter

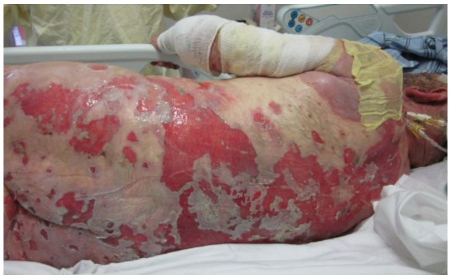
PEMPHIGUS VULGARIS

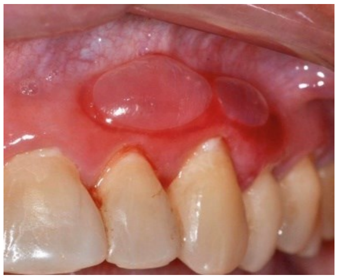
MORPHOLOGY

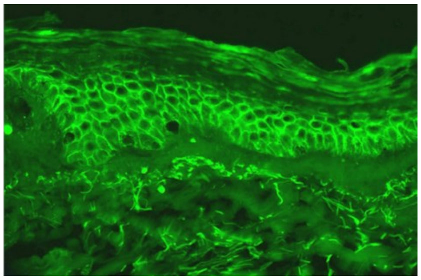
- May show **intraepidermal vesicles** with **eosinophilic spongiosis** in early stages
- Well-developed lesions show **intraepidermal split** immediately above basal layer leaving a **tombstone** row of basal keratinocytes
- **Follicular extension** of acantholysis
- Superficial **perivascular and interstitial** lymphocytes and eosinophils

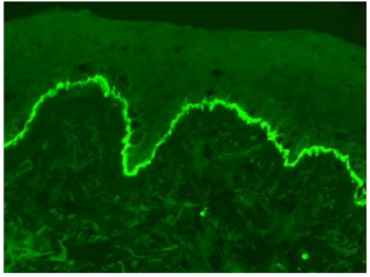
OTHER HIGH YIELD POINTS

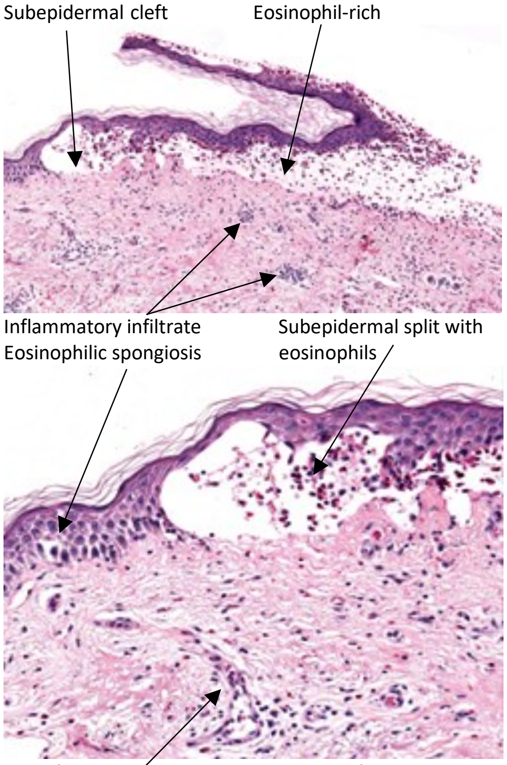
- Clinically **painful flaccid blisters and erosions** – involving the skin as well as **mucosa**, including **oral mucosa**, esophagus, conjunctiva, nasal mucosa, vagina, labia, anus.
- Positive **Nikolsky sign**: extension of the epidermis laterally with slight pressure/rubbing.
- Most common type of pemphigus
- Autoantibodies directed against **desmoglein 1 and/or 3**
- Direct immunofluorescence - IgG and C3 in a **chicken-wire / net-like pattern**
- IIF and ELISA detect antibodies.


Painful flaccid blisters


Almost always involves oral mucosa


PV: Direct DIF- net-like pattern with IgG and C3


Bullous Pemphigoid: Linear IgG in DEJ


Subepidermal cleft
Eosinophil-rich
Inflammatory infiltrate
Eosinophilic spongiosis
Subepidermal split with eosinophils
Superficial perivascular and interstitial inflammatory infiltrate of lymphocytes and eosinophils

Immunoflorescence:

A. Bullous Pemphigoid: Linear staining of IgG at DEJ

B. Pemphigus Vulgaris: IgG and C3 in a chicken-wire / net-like pattern

C. Dermatitis Herpetiformis: Granular IgA in dermal papillae on DIF

D. Linear IgA: Linear IgA at DEJ (not shown)

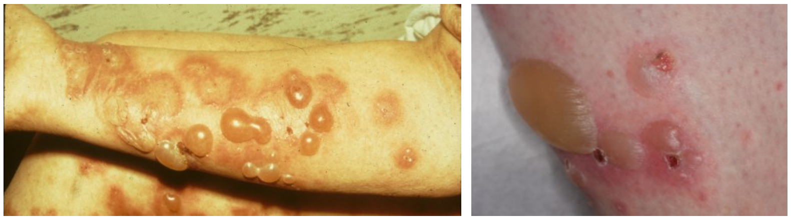
BULLOUS PEMPHIGOID (BP)

MORPHOLOGY

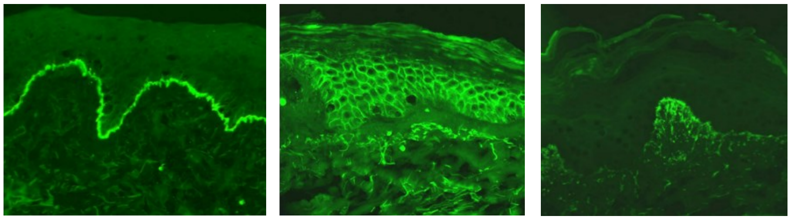
- **Subepidermal blister** with **eosinophils**
- At the edge of the blister, **eosinophilic spongiosis** is often seen
- A superficial **perivascular and interstitial** inflammatory infiltrate of lymphocytes and eosinophils is present in the dermis
- The **urticarial** variant clinically of BP may only demonstrate eosinophilic spongiosis on biopsy

OTHER HIGH YIELD POINTS

- Clinically, symmetric, **tense bullae, exquisitely pruritic, crusting erosions**
- Usually affects **older adults**
- Direct **immunofluorescence shows linear deposition** of IgG and C3 at dermoepidermal junction (DEJ) In the perilesional skin
- Autoantibodies to **BPAG1 and BPAG2 on hemidesmosomes** at DEJ
- Drug-induced pemphigoid: diuretics (furosemide), captopril, amoxicillin etc.
- Salt-split skin distinguishes between BP and epidermolysis bullosa acquisita

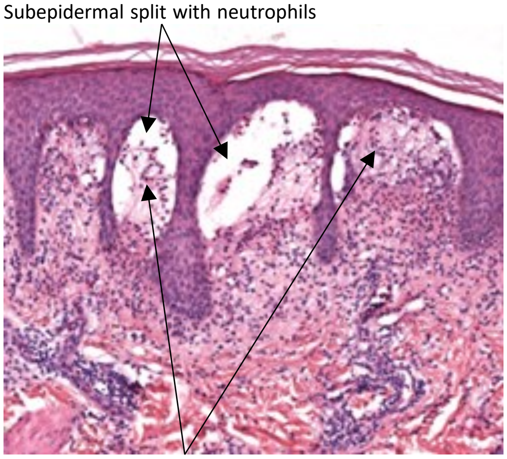


Bullous Pemphigoid: Pruritic tense bullae, with crusting erosions



A: Bullous Pemphigoid B: Pemphigus Vulgaris C. Dermatitis Herpetiformis

Path Presenter


Subepidermal split with neutrophils
Papillary dermal microabscesses

DERMATITIS HERPETIFORMIS

MORPHOLOGY

- Subepidermal split with numerous neutrophils, and rare eosinophils
- **Papillary dermal microabscesses**

OTHER HIGH YIELD POINTS

- Clinically, symmetrically involves elbows, knees, back of neck, sacrum, posterior scalp, with urticarial papules/plaques
- intense pruritus, excoriations/erosions
- Highly associated with **Celiac disease**/ gluten-sensitive enteropathy
- **Granular IgA** in dermal papillae on DIF
- **IgA** antibodies to gluten-**tissue transglutaminase** (t-TG), which is found in the gut.

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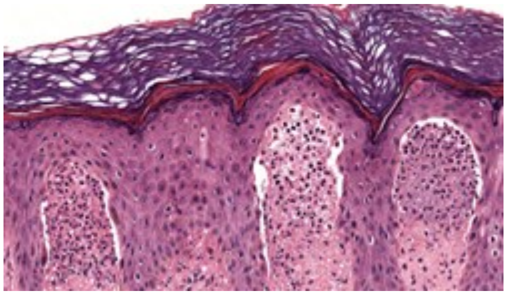
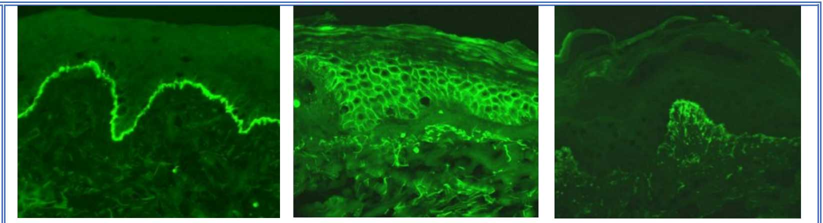


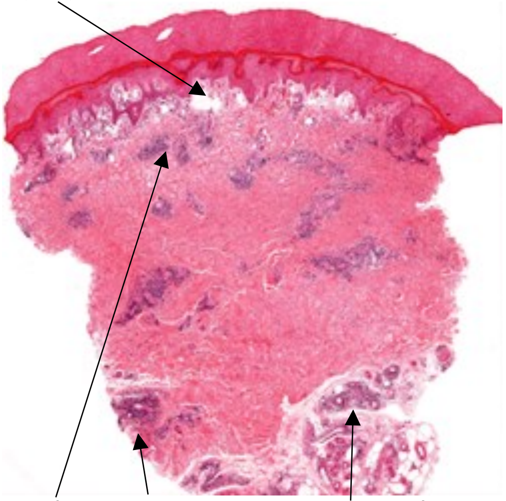
Papillary dermal microabscesses, numerous neutrophils



A: Bullous Pemphigoid B: Pemphigus Vulgaris C. Dermatitis Herpetiformis

A. Bullous Pemphigoid: Linear staining of IgG at DEJ
B. Pemphigus Vulgaris: IgG and C3 in a chicken-wire / net-like pattern
C. Dermatitis Herpetiformis: Granular IgA in dermal papillae on DIF

VASCULITIS AND VASCULOPATHY



Papillary dermal edema

Superficial & deep perivascular & peri eccrine infiltrate

Path Presenter

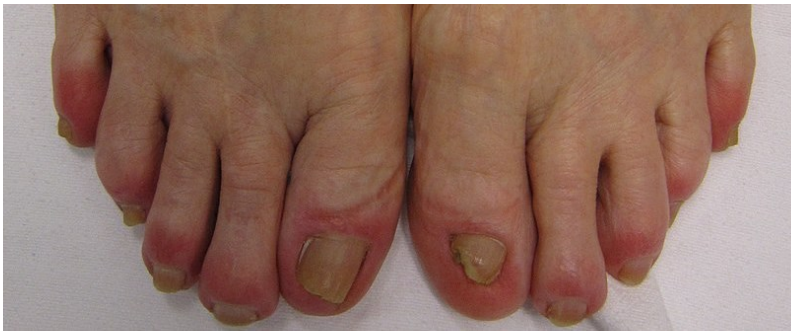
PERNIO

MORPHOLOGY

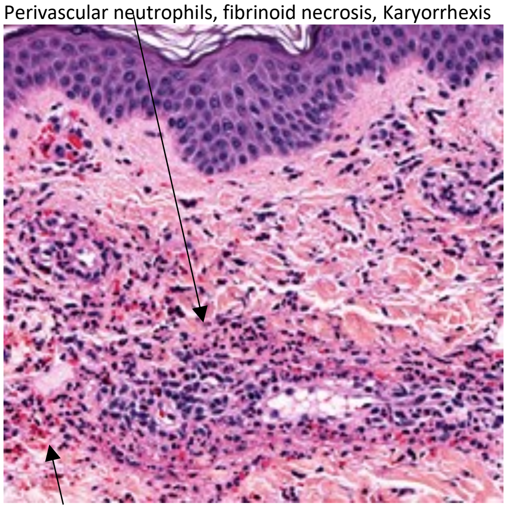
- Superficial and deep perivascular infiltrate of lymphocytes
- Prominent peri eccrine inflammatory infiltrates
- **Papillary dermal edema**

OTHER HIGH YIELD POINTS

- aka chilblains
- Caused by **exposure to cold**, damp conditions
- Tender violaceous papules mostly on **acral skin**, ears, and nose
- Most common association is with systemic lupus erythematosus



Perivascular neutrophils, fibrinoid necrosis, Karyorrhexis



RBCs extravasation

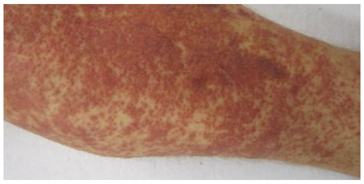
LEUKOCYTOCLASTIC VASCULITIS

MORPHOLOGY

- **Fibrinoid necrosis** of vessel walls
- Endothelial cell swelling
- Perivascular neutrophilic infiltrate
- **Karyorrhexis (leukocytoclasia**, nuclear dust)
- RBCs extravasation

OTHER HIGH YIELD POINTS

- Clinically, non-blanching **palpable purpura**, mostly on **lower legs**
- Immune complexes deposition in blood vessel walls
- Differential diagnosis – Atrophie blanche/ livedoid vasculopathy



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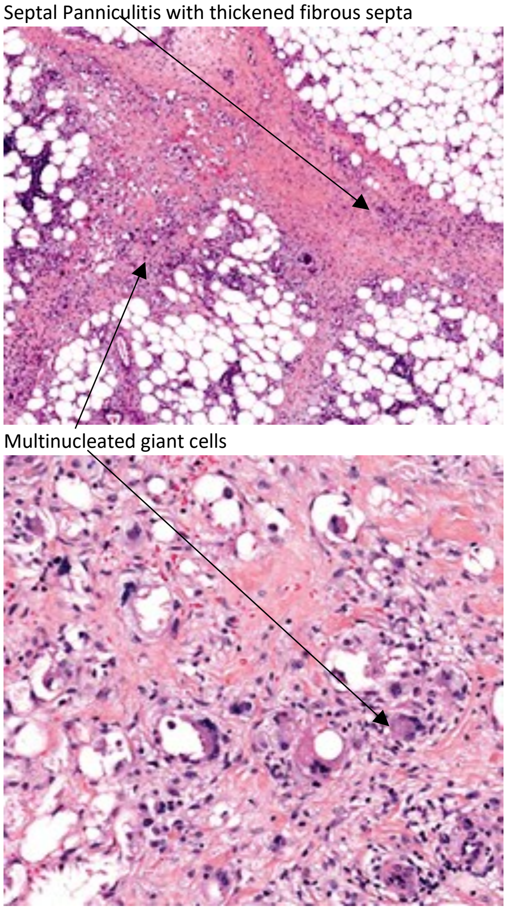
9. SKIN PATHOLOGY

PANNICULITIDES


Septal Panniculitis with thickened fibrous septa
Multinucleated giant cells

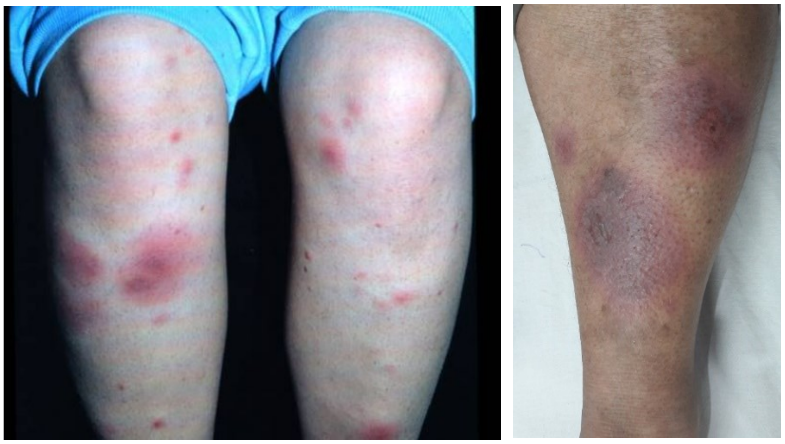
ERYTHEMA NODOSUM

MORPHOLOGY

- **Septal Panniculitis**
- **Thickening** of fibrous septa, with lymphohistiocytic infiltrate
- Multinucleated **giant cells**, granulomas/lipogranulomas/**Miescher radial granulomas**

OTHER HIGH YIELD POINTS

- Clinically, red, **tender nodules on the pretibial area**
- Most often in young to middle-aged females
- Associated with **infection as well as drugs**
- Systemic symptoms may be present
- Differential diagnosis – erythema induratum (lobular panniculitis)



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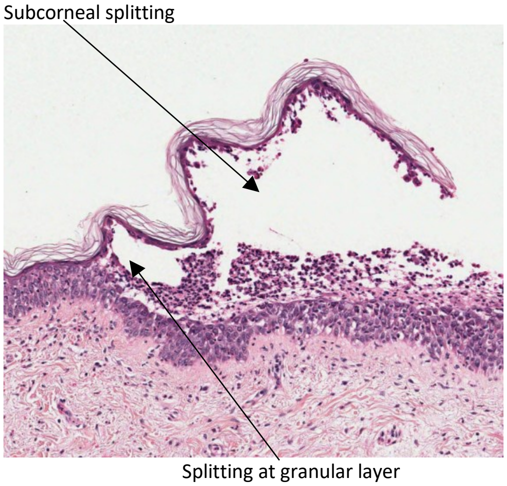
BACTERIAL INFECTIONS


Subcorneal splitting
Splitting at granular layer

Path Presenter

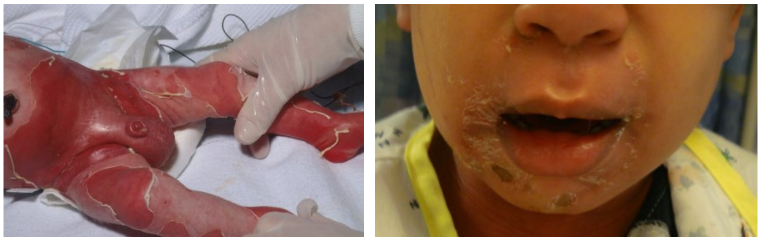
STAPHYLOCOCCAL SCALDED SKIN SYNDROME

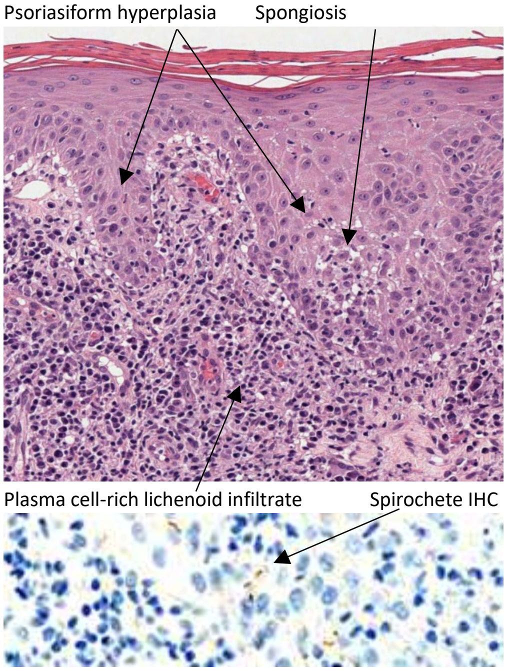
MORPHOLOGY

- **Subcorneal splitting** of epidermis at granular layer

OTHER HIGH YIELD POINTS

- Extremely tender flaccid blisters in infants and young children
- Usually resolves spontaneously
- Due to **exfoliatin A and B from strains of Staphylococcus aureus**
- Differential diagnosis-
  - Bullous Impetigo – direct infection, cocci present
  - Toxic Epidermal Necrolysis – subepidermal split
  - Pemphigus Foliaceous – DIF positive




Psoriasiform hyperplasia
Spongiosis
Plasma cell-rich lichenoid infiltrate
Spirochete IHC

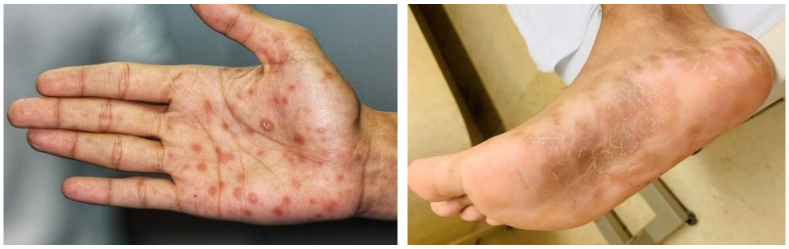
SYPHILIS

MORPHOLOGY

- Great mimicker - variable histology
- Usually **psoriasiform hyperplasia, spongiosis, and interface changes**
- **Plasma cell-rich infiltrate,** sometimes **lichenoid**

OTHER HIGH YIELD POINTS

- Secondary syphilis (SS) occurs 1-2 months after primary chancre
- Maculopapular patches or plaques usually involving **palms and soles**
- **Spirochete immunostain is positive**
- Warthin-Starry silver stains and PCR – less sensitive



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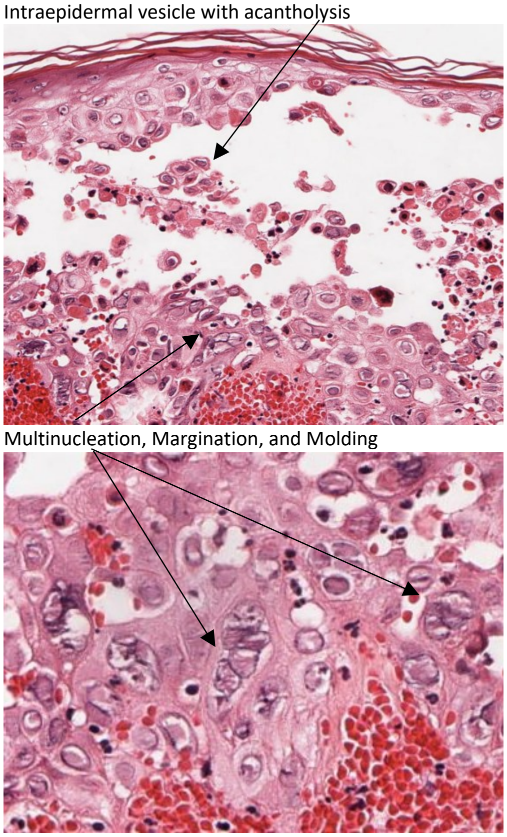
VIRAL INFECTIONS


Intraepidermal vesicle with acantholysis
Multinucleation, Margination, and Molding

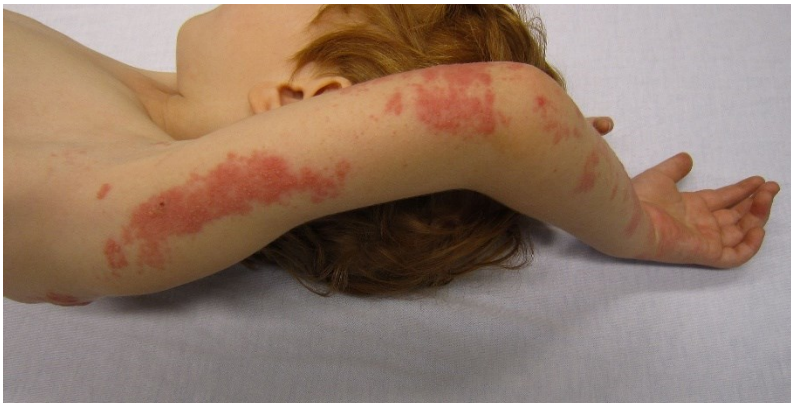
HERPESVIRUS/ HERPES ZOSTER/ VARICELLA

MORPHOLOGY

- **Intraepidermal vesicle** with acantholysis and ballooning of keratinocytes
- **3M - Multinucleation, Margination, and Molding** of nucleus

OTHER HIGH YIELD POINTS

- HSV – **Clear, fluid-filled vesicles**
- Herpes Zoster – fever and malaise followed by **grouped vesicles** in dermatome distribution
- Varicella – vesicles at different stages
- **HSV-1, HSV-2, or VZV** immunostain positive
- DIF, In-situ hybridization, serologic testing and PCR can be done



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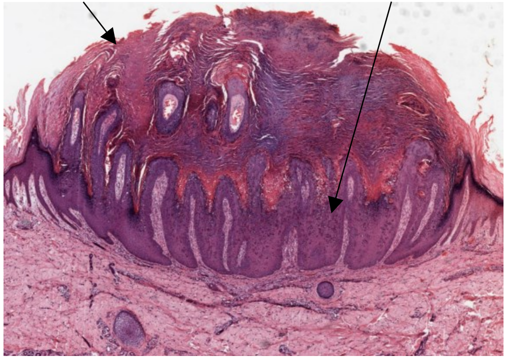
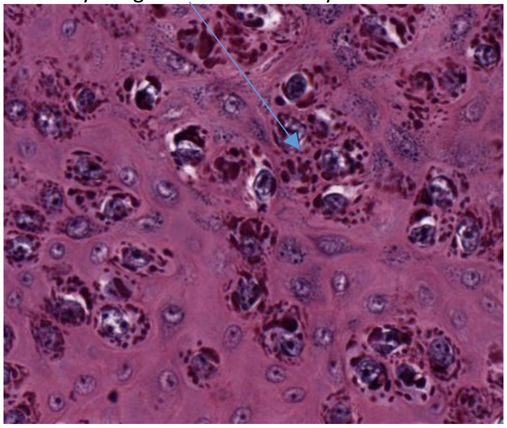


Keratohyalin granules and Koilocytes



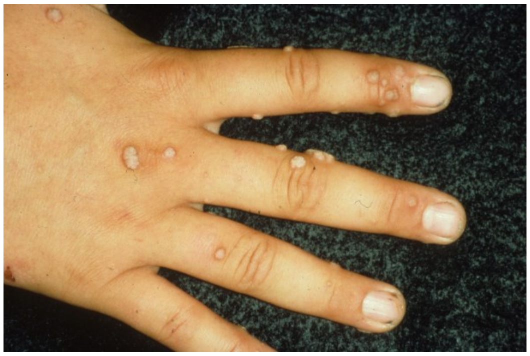
VERRUCA VULGARIS (VV)

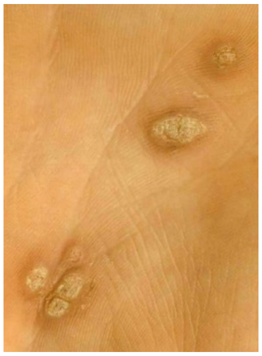
MORPHOLOGY

- Cup shaped papillomatosis
- Mounds of parakeratosis (**church spires**)
- Prominent keratohyalin granules and **koilocytes**

OTHER HIGH YIELD POINTS

- Mostly involves fingers and dorsal hands (VV), and palms and soles (palmoplantar wart) of children
- Variants – Common wart (VV), Palmoplantar wart (Myrmecia) and Flat wart (verruca plana)
- Due to HPV – most common types include 1, 2, 3, 4, 7, and 10
- **Condyloma acuminatum** – Other HPV related lesion (**HPV 6,11**) involving genitalia





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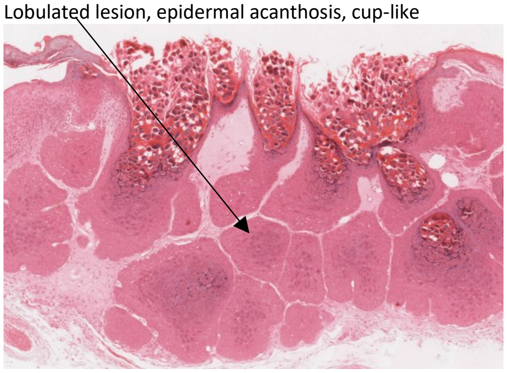
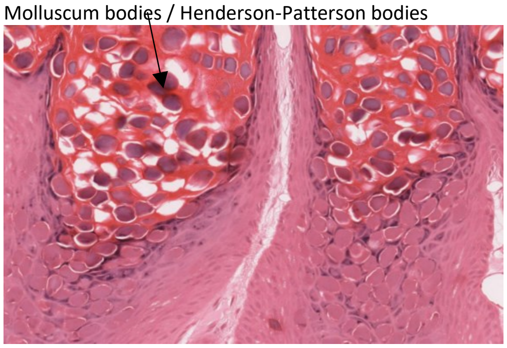
Lobulated lesion, epidermal acanthosis, cup-like



Molluscum bodies / Henderson-Patterson bodies



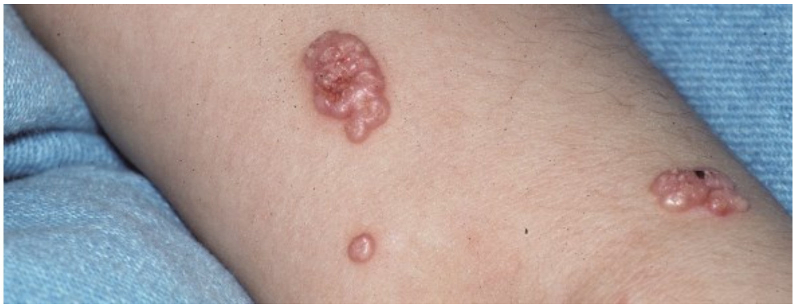
MOLLUSCUM CONTAGIOSUM

MORPHOLOGY

- Crater with distinct **Molluscum bodies/Henderson-Patterson bodies** (eosinophilic to basophilic large intracytoplasmic inclusions)
- Epidermal acanthosis with **cup-shaped lesion**
- Low power: **lobulated**, well-circumscribed, somewhat crateriform intradermal pseudotumor-like lesion

OTHER HIGH YIELD POINTS

- Clinically, pearly papules with **central umbilication** in young children
- Caused by **Molluscum contagiosum virus (Poxvirus)**



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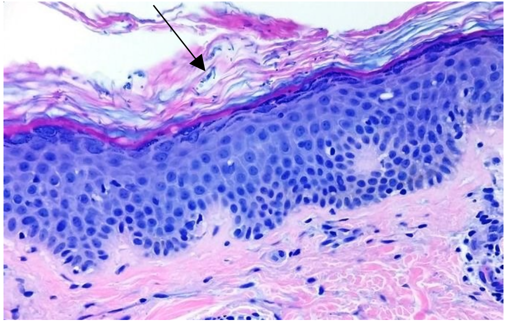
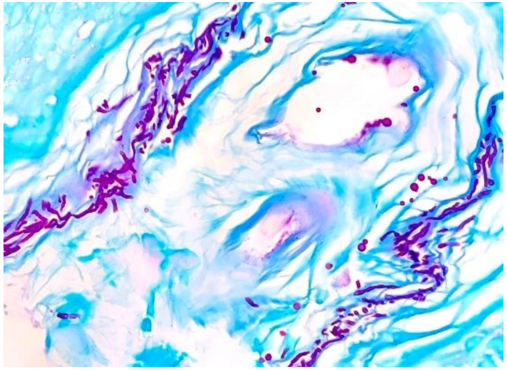
FUNGAL INFECTIONS

Fungal hyphae in stratum corneum



Courtesy: Dutch Berry, MD



PAS stain highlighting fungal hyphae ©Mary Landau, MD

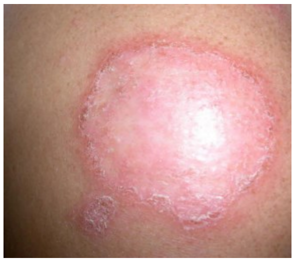
DERMATOPHYTOSIS/TINEA

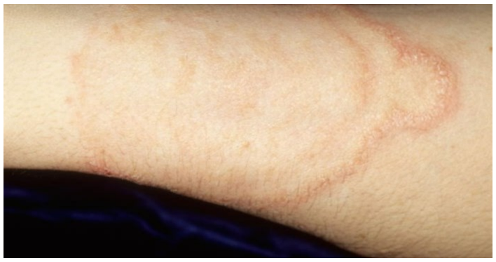
MORPHOLOGY

- **Hyphae in stratum corneum**
- Psoriasiform hyperplasia and/or spongiosis
- Mild to moderate inflammation usually with some **neutrophils**
- Neutrophils in the cornified layer
- **Sandwich sign**: neutrophils between layers of orthokeratosis or parakeratosis

OTHER HIGH YIELD POINTS

- Clinically, annular plaque with scale at border
- **PAS or GMS highlights hyphae**
- Infection by dermatophytes – Trichophyton, Epidermophyton, and Microsporum
- **Majocchi granuloma** – Fungal hyphae extending into hair follicles'





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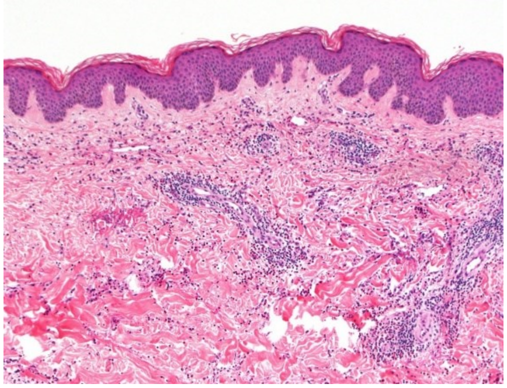
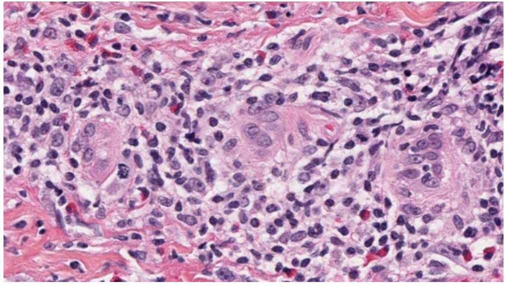
ARTHROPODS

Wedge-shaped infiltrate rich in eosinophils



Perivascular infiltrate with lymphocytes and eosinophils



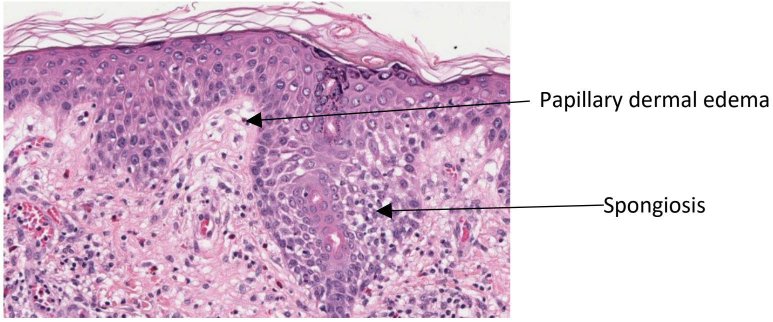
ARTHROPOD BITE REACTION

MORPHOLOGY

- **Wedge-shaped** perivascular lymphocytic **infiltrate with eosinophils**
- **Insect bites** - prominent papillary dermal edema, spongiosis, blister, epidermal necrosis
- **Tick bite** - mouth part may be seen
- **Spider bites** - more neutrophils

OTHER HIGH YIELD POINTS

- Clinically variable presentations - erythematous papule, plaque, nodule, vesicle, or bulla
- Hypersensitivity reaction



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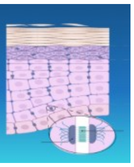
9. SKIN PATHOLOGY



SCABIES

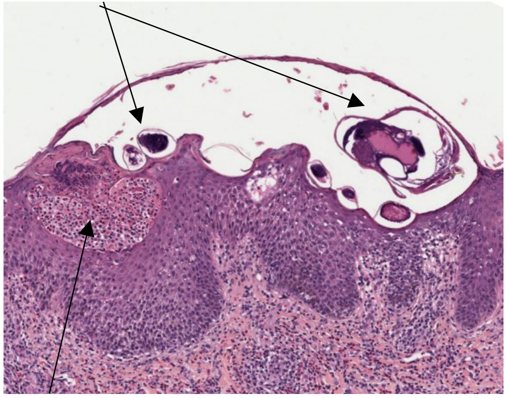
MORPHOLOGY

- Scabies mite, ova or scybala is found within the stratum corneum
- Spongiosis and eosinophilic spongiosis may be present to varying degrees within the epidermis
- In the dermis, a superficial and deep perivascular and interstitial inflammatory infiltrate is present with prominent numbers of eosinophils

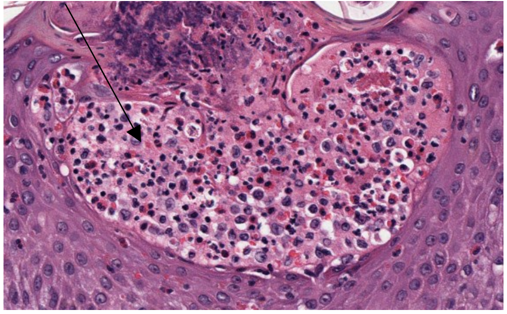
OTHER HIGH YIELD POINTS

- Usually involves interdigital areas, flexures, and intergluteal folds
- Papulovesicular, nodules or Norwegian (crusted)
- Caused by **Sarcoptes scabiei**

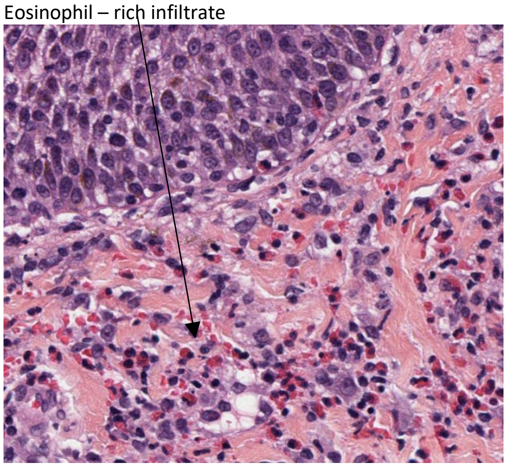
Mite, feces, or eggs in stratum corneum

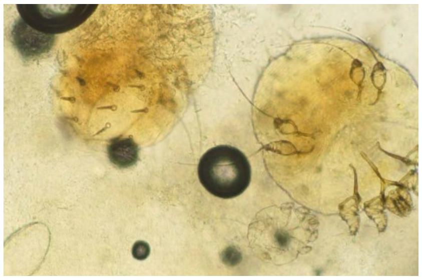


Eosinophilic Spongiosis

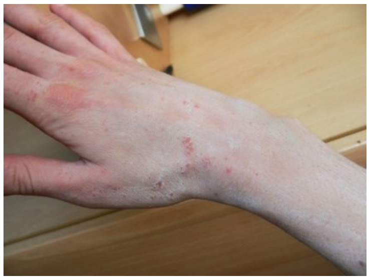


Eosinophil – rich infiltrate

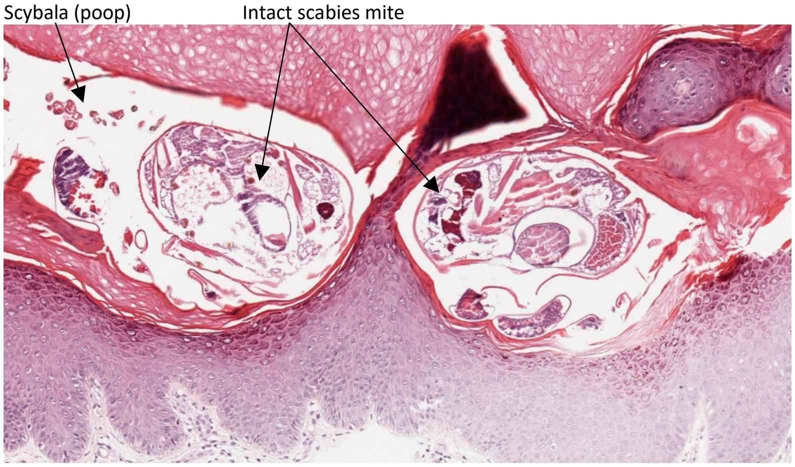




Scabies mite



Flexural papulovesicular rashes



Path Presenter

NEOPLASTIC DERMATOPATHOLOGY

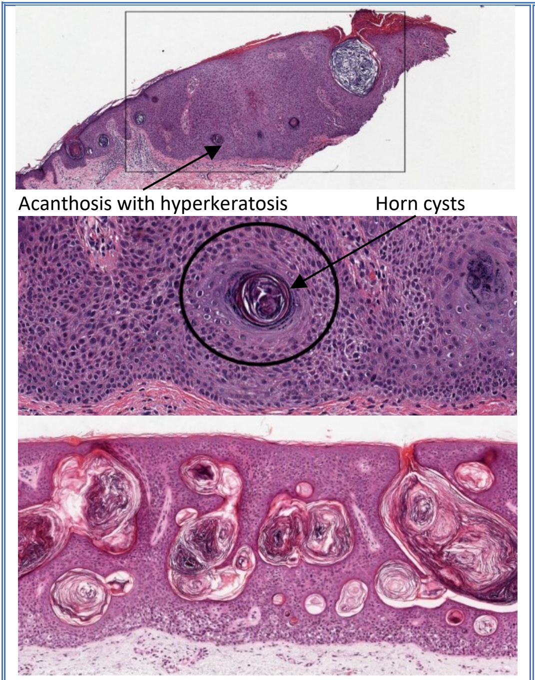
WHO CLASSIFICATION OF SKIN TUMORS

- Keratinocytic tumors
- Appendageal tumors
- Melanocytic tumors
- Other (soft tissue tumors and tumors of hematopoietic and lymphoid origin)

KERATINOCYTIC TUMORS/LESIONS AND CYSTS

- Seborrheic keratosis
- Solar lentigo
- Epidermal inclusion cyst (EIC)
- Dermoid cyst
- Pilar/Trichilemmal cyst
- Verruca vulgaris
- Actinic keratosis
- Squamous cell carcinoma in situ (SCCIS, Bowen disease)
- Squamous cell carcinoma (SCC)

- Basal cell carcinoma (BCC)
- Merkel cell carcinoma


Acanthosis with hyperkeratosis
Horn cysts

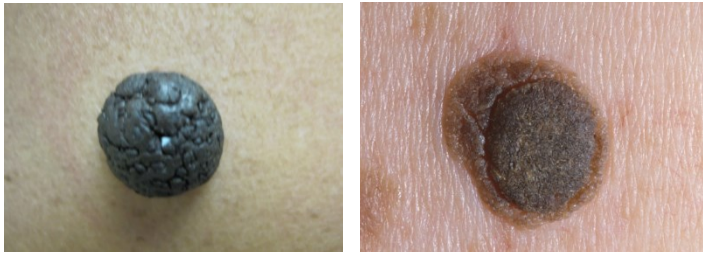
SEBORRHEIC KERATOSIS

MORPHOLOGY

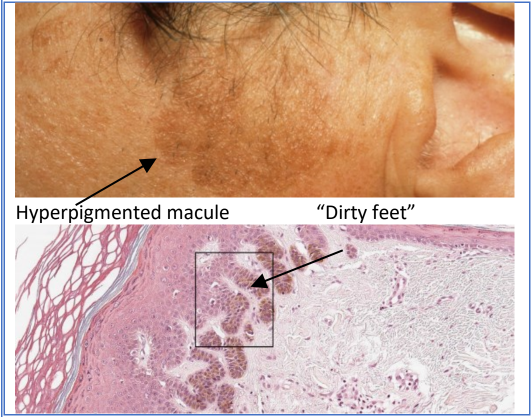
- Clinical: Brown, waxy “stuck-on” papule
- Microscopy: **Acanthosis with hyperkeratosis** and hyperpigmentation, anastomosing rete, **horn cysts** with lamellated keratin, and without atypia

OTHER HIGH YIELD POINTS

- Intraepidermal basaloid keratinocytic proliferation with multiple variants (no clinical or prognostic significance)
- Common in the middle-aged and elderly with incidence increasing with age
- Leser-Trélat sign: Paraneoplastic phenomenon of rapid growth of multiple seborrheic keratoses associated with gastrointestinal adenocarcinoma



Path Presenter


Hyperpigmented macule
“Dirty feet”

SOLAR LENTIGO

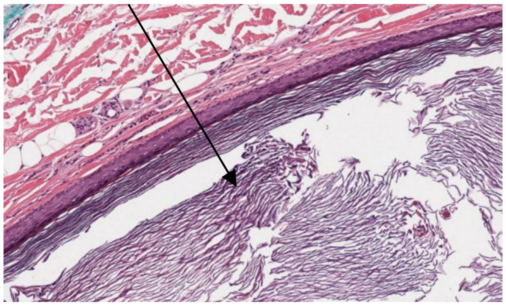
MORPHOLOGY

- Clinical: **Hyperpigmented macule**
- Microscopy: **“Dirty feet”** or finger-like proliferation of hyperpigmented rete growing down from the epidermis

OTHER HIGH YIELD POINTS

- Accumulation of melanin in keratinocytes due to sun exposure
- Also known as age spot and found on sun-exposed skin of the elderly
- Pigmentation may be irregular, and there may be solar elastosis and some chronic inflammation in the dermis

Path Presenter


Squamous-lined cyst with granular layer and containing laminated keratin

EPIDERMAL INCLUSION CYST (EIC)

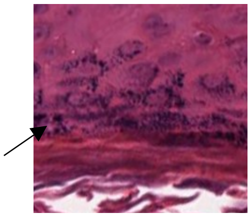
MORPHOLOGY

- Gross: Subcutaneous cyst filled with thick yellow keratinaceous debris
- Microscopy: Lined by **squamous epithelium with granular layer and containing laminated (basket weave) keratin**

OTHER HIGH YIELD POINTS

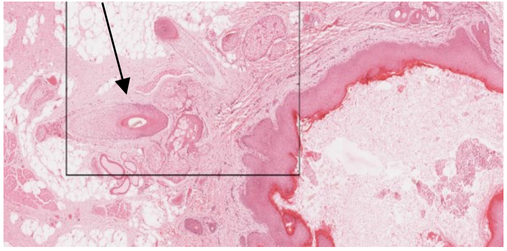
- Acquired unilocular cyst due to trauma
- May rupture and become inflamed

Path Presenter


Granular layer

9. SKIN PATHOLOGY

Hair follicles and sebaceous glands in the cyst wall



DERMOID CYST

MORPHOLOGY

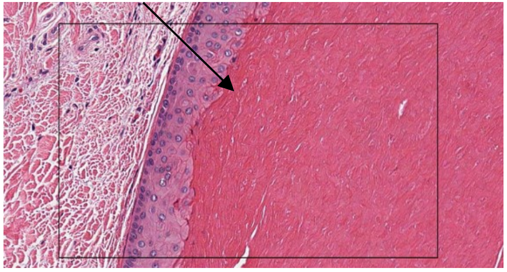
- Like EIC, but with **hair follicles and sebaceous glands**

OTHER HIGH YIELD POINTS

- Present at birth

Path Presenter

Dense “wet” keratin with absent granular layer



PILAR/TRICHILEMMAL CYST

MORPHOLOGY

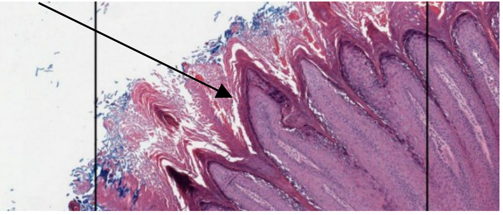
- Filled with **dense, “wet” eosinophilic keratin**
- Stratified squamous epithelium with an **absent granular layer**

OTHER HIGH YIELD POINTS

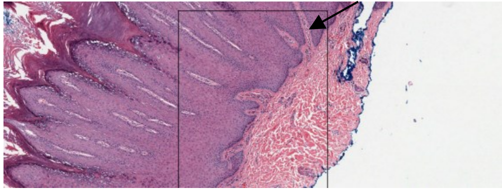
- Scalp/head and neck location

Path Presenter

“Church spire” papillae



“Cup-like” rete ridges



VERRUCA VULGARIS

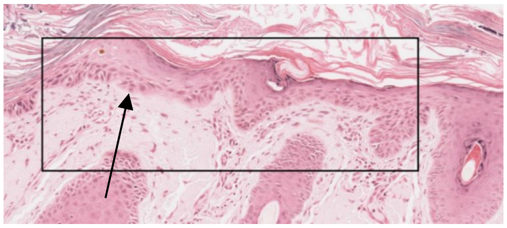
MORPHOLOGY

- Clinical: Flesh-colored papule with a rough surface
- Microscopy: **“Church spire” papillae,** tiered parakeratosis, **“Cup-like” rete** with inward bending of rete at the base of the lesion, and increased vasculature in the papillary dermis (bleed easily)

OTHER HIGH YIELD POINTS

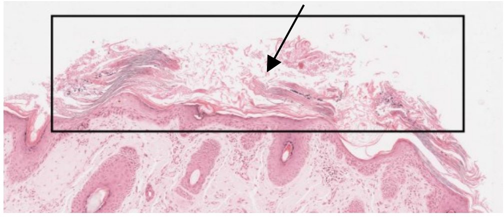
- HPV-induced, circumscribed lesion
- Koilocytes or vacuolated keratinocytes with raisin-like nuclei may be variably present
- Verruca plana = flat wart

Path Presenter



Basal atypia

“Flag sign”



ACTINIC KERATOSIS

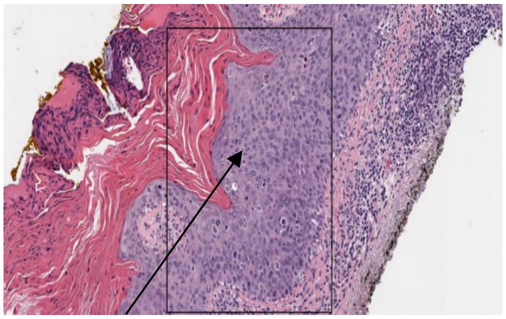
MORPHOLOGY

- Clinical: Erythematous, rough, scaly plaque, macule, or papule; often multiple
- Microscopy: **Basal atypia** limited to the lower third of the epidermis with **“Flag sign”** of alternating orthokeratosis and parakeratosis and solar elastosis in the dermis

OTHER HIGH YIELD POINTS

- Intraepidermal keratinocytic lesion due to sun damage
- Precancerous, risk of malignancy (progression to SCC) is ~8-20% per year
- Sparing of cutaneous adnexa in most circumstances, if extending down the hair follicle and sweat duct -> proliferative actinic keratosis

Path Presenter



Full thickness dysplasia with loss of the granular layer; can have a pagetoid appearance

SQUAMOUS CELL CARCINOMA IN-SITU (SCCIS OR BOWEN DISEASE)

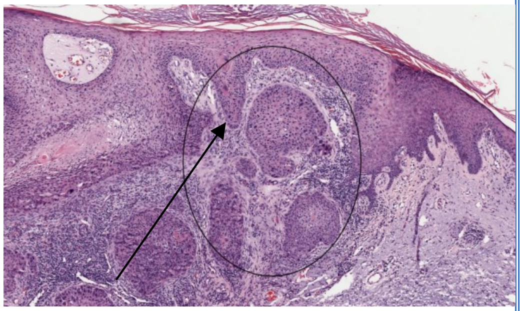
MORPHOLOGY

- **Full thickness dysplasia** of the epidermis without invasion -> Loss of granular layer
- Can have a **pagetoid appearance**

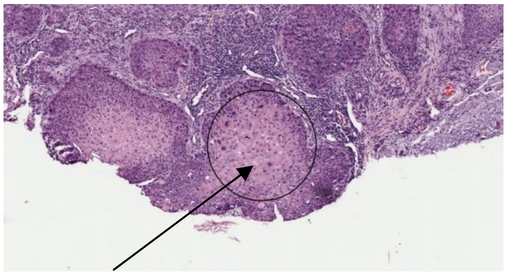
OTHER HIGH YIELD POINTS

- No epidermal maturation
- Epidermis appears disorganized
- Important differential is Paget disease and melanoma

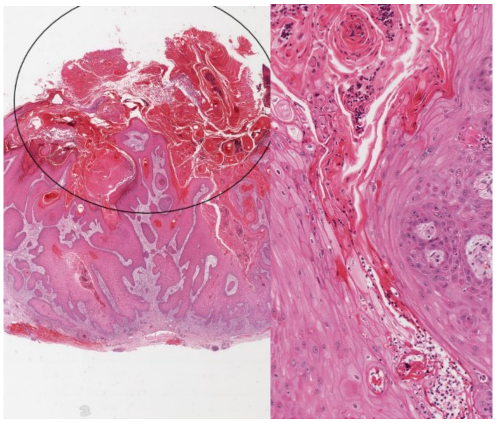
Path Presenter



Squamous nests arising from the epidermis and invading the dermis



Deep keratinization



Keratoacanthoma type with crateriform architecture (circled, left) and glassy, pale pink cytoplasm (right)

SQUAMOUS CELL CARCINOMA (SCC)

MORPHOLOGY

- Nests of atypical squamous cells arise from the epidermis and **invade the dermis**
- Findings that suggest invasion
  - Jagged interface with dermis
  - Aberrant **deep keratinization**
  - Single cells invasion
- Evidence of squamous differentiation (keratinization and intercellular bridges)
    - Dyskeratotic cells = squamous differentiation
- Often associated with AK or SCCIS

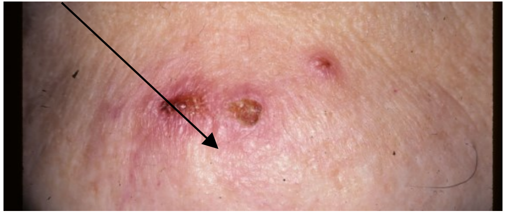
OTHER HIGH YIELD POINTS

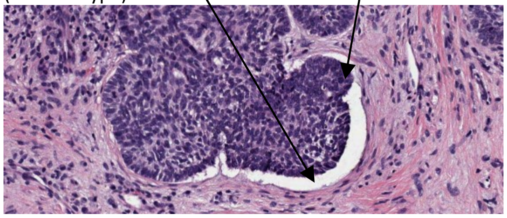
- Second most common form of skin cancer (20% of cutaneous malignancies)
- Locally destructive; metastatic potential
  - Risk factors for metastasis (high risk): location (ear, lip), size (>2cm), depth, evidence of perineural invasion, evidence of desmoplastic features
- Tx: Depends on size, location, and depth of invasion: Excision, Mohs micrographic surgery, Radiation
- Variants:
  - *Keratoacanthoma* - well-differentiated variant of SCC that spontaneously regresses in most cases. Typically composed of large, **crateriform** (cup-like) lesion filled with abundant keratin debris and composed of cells with **glassy, pale pink cytoplasm**
  - *Acantholytic SCC* – acantholysis with large epithelioid cells with dense eosinophilic cytoplasm and scattered dyskeratotic (apoptotic) cells
  - *Verrucous SCC* – Extremely well-differentiated, low-risk with pushing border and acanthotic papilla. NO infiltrative growth. Associated inflammation at base.
  - *Desmoplastic SCC* – tumor cells become spindled/sarcomatoid

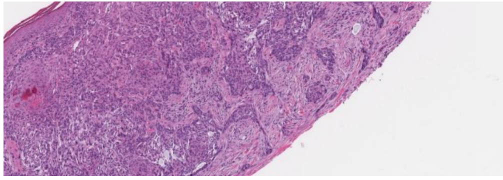
- *HMWCKs, p63, and p40 are the most sensitive markers for poorly differentiated and spindle cell/sarcomatoid SCC (Pankeratin can be lost in poorly differentiated and spindle cell tumors)

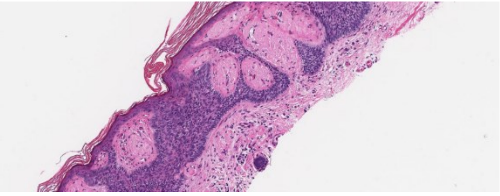
Path Presenter

9. SKIN PATHOLOGY


Pearly pink/tan papule


Basaloid cells with retraction and peripheral palisading (nodular type)


Infiltrative type


Fibroepithelioma of Pinkus

BASAL CELL CARCINOMA

MORPHOLOGY

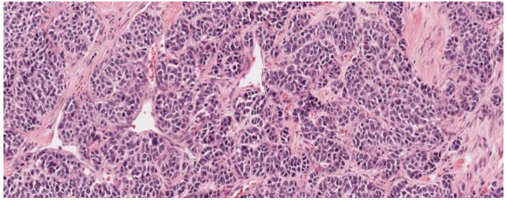
- Clinical: Nodular variant presents as a pearly papule, often with telangiectasia and/or ulceration
- Microscopy: Basaloid appearance at low power (high N:C ratio) often with an epidermal connection, **peripheral palisading, and retraction from the surrounding stroma**
- Many subtypes that vary in morphology
  - ➢ Nodular – Large, rounded nests
  - ➢ Micronodular* – smaller nests
  - ➢ Superficial – superficial nests separated by uninvolved areas
  - ➢ Infiltrative*- small infiltrative cords
  - ➢ Sclerosing/morpheic* - infiltrative nests with desmoplastic stroma
  - ➢ Basosquamous* - Prominent areas of squamous differentiation
  - ➢ Infundibulocystic – resemble hair follicle
  - ➢ Fibroepithelioma of Pinkus – anastomosing cords

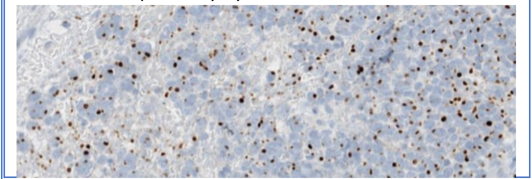
*Aggressive variants

OTHER HIGH YIELD POINTS

- Most common malignancy in humans
- Locally aggressive and destructive behavior
- Very low metastatic potential (< 0.1%)
- Pediatric BCC? -> consider Gorlin's Syndrome
- Note: Some focal keratinization may be present
- May mimic adnexal structures, making margins challenging. However, basal cell carcinoma tumor cells should have darker chromatin, more apoptosis and mitoses, and paler cytoplasm than the hair follicles.
- IHC: BerEP4 will stain BCC but not SCC

Path Presenter


Dermal tumor composed of basaloid islands of cells


Dot-like CK20 positivity by IHC

MERKEL CELL CARCINOMA

MORPHOLOGY

- Cutaneous neuroendocrine carcinoma
- Dermal-based tumor with **basaloid islands in the dermis**
- Can resemble BCC on low power
- Composed of cells with salt and pepper chromatin

OTHER HIGH YIELD POINTS

- High mitotic rate and apoptotic index
- **Dot-like CK20 positivity**
- **P63**+ have a worse prognosis

Path Presenter

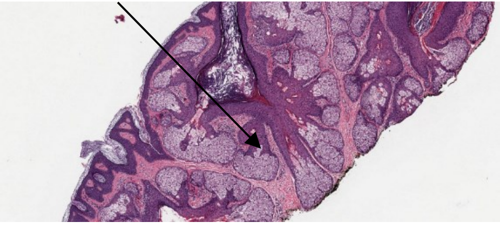
APPENDAGEAL TUMORS

SEBACEOUS, FOLLICULAR, AND APOCRINE/ECCRINE TUMORS

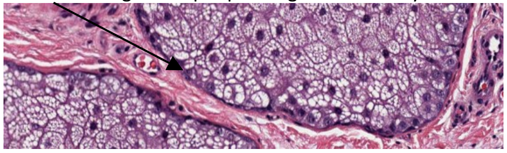
- Sebaceous hyperplasia
- Sebaceous adenoma
- Sebaceous carcinoma
- Nevus sebaceus of Jadassohn
- Trichofolliculoma
- Chondroid syringoma
- Eccrine poroma
- Hidradenoma papilliferum
- Syringocystadenoma papilliferum
- Acrospiroma
- Spiradenoma

- Trichilemmoma
- Pilomatrixoma (Calcifying Epithelioma of Malherbe)
- Tumor of follicular infundibulum
- Trichoepithelioma
- Fibrofolliculoma/Trichodiscoma
- Cylindroma
- Syringoma
- Microcystic adnexal carcinoma
- Extramammary Paget's disease (EMPD)

Sebocyte lobules arranged around the infundibulum



No thickening of the peripheral germinative layer



SEBACEOUS HYPERPLASIA

MORPHOLOGY

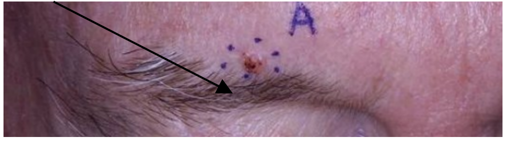
- Clinical: yellow papule with a central dimple
- Microscopic: Lobules of sebocytes are arranged around the infundibulum of a **central hair follicle without thickening of the peripheral germinative layer**

OTHER HIGH YIELD POINTS

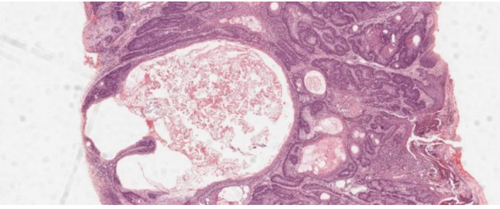
- Nose or cheeks of the elderly
- Umbilicated yellowish papules
- No cytologic atypia

Path Presenter

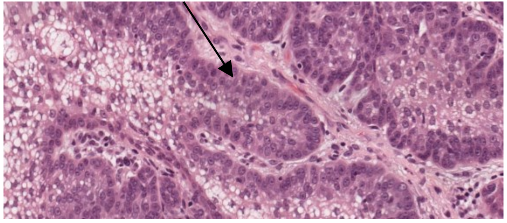
Ulcerated papule



multilobulated proliferation of sebaceous glands



Expansion of the peripheral germinative layer (<50%)



SEBACEOUS ADENOMA

MORPHOLOGY

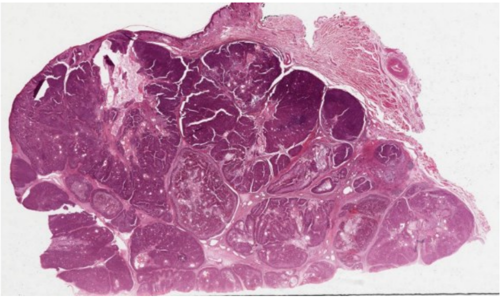
- Clinical: **ulcerated papule,** mostly in the **head and neck,** particularly on the **face and scalp**
- Microscopic: well-circumscribed, **multilobulated proliferation of sebaceous glands with expansion of the peripheral germinative layer of more than 2 layers (<50%)**

OTHER HIGH YIELD POINTS

- Similar low power look to sebaceous hyperplasia but larger nodular aggregates with downward growth from epidermis
- Predominance (> 50%) of sebocytes. Cytologic atypia not prominent
  - Composed of > 50% germinative/basaloid cells -> Sebaceoma (still has a well-circumscribed lobulated appearance)
- Associated with **Muir Torre** if multiple in younger patients <50 yo
  - AD form of Lynch syndrome
  - Mutations in one of the DNA mismatch repair genes, MLH1, MSH2, MSH6
  - Associated with gastrointestinal carcinomas and KAs of skin

Path Presenter

Infiltrative appearance



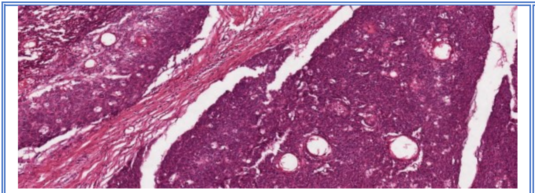
SEBACEOUS CARCINOMA

MORPHOLOGY

- Microscopic: **>50% expansion** of the peripheral germinative layer with necrosis and a more infiltrative appearance
- Clear cells often present but vary greatly in number
- Show prominent **cytologic atypia and pleomorphism**
- Mitotic figures, including atypical forms, are usually abundant
- IHC: May stain with Adipophilin, AR, EMA, and Factor XIIIa

OTHER HIGH YIELD POINTS

- Aggressive tumors with a high incidence of metastasis (> 30%)
- Strong association with Muir-Torre syndrome if patients have multiple

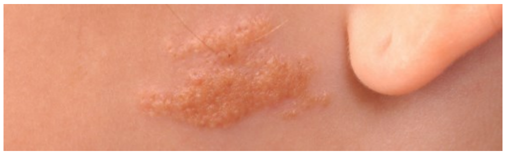


Expansion of the peripheral germinative layer (>50%)

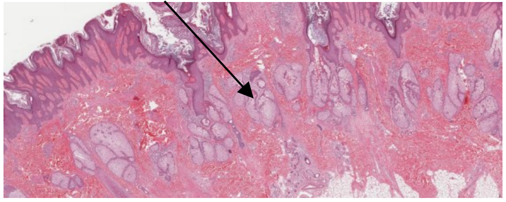
- Sebaceous tumors (Genes implicated include MLH1, MSH2, MSH6, PMS2)
- Eyelids are the most common site (~ 75% of cases)
- Periocular or extraocular

Path Presenter

“Cobblestone” lesion



Hamartoma of excess sebaceous glands high in the dermis with overlying alopecia



NEVUS SEBACEOUS OF JADASSOHN (ORGANOID NEVUS)

MORPHOLOGY

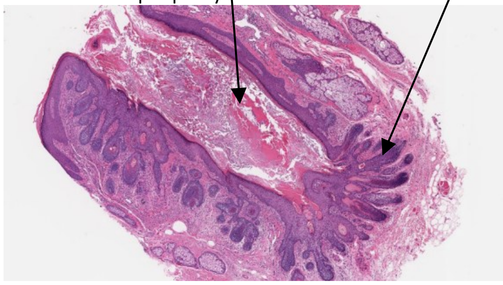
- Clinical: **“Cobblestone” greasy-appearing lesion**
- Microscopic: **Hamartoma of excess sebaceous glands,** absent or abortive hair follicles, and **dilated ectopic apocrine glands**

OTHER HIGH YIELD POINTS

- Present at birth on the head and neck
- Cerebriform looking initially, then more verrucoid during puberty
- In older adults, you can see other tumors arising in them like syringocystadenoma papilliferum, trichilemmoma, and basal cell carcinoma

Path Presenter

Centrally dilated hair follicle with primitive smaller hair follicles in the periphery



TRICHOFOLLICULOMA

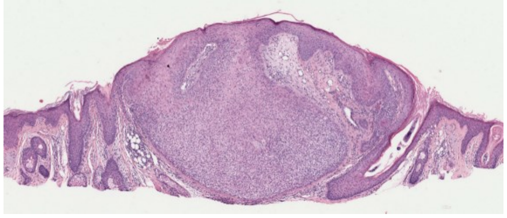
MORPHOLOGY

- **Centrally dilated hair follicle filled with keratinaceous debris** and lined by squamous epithelium with a thin granular layer and dilated hair follicles that have several **radiating primitive smaller hair follicles in the periphery**

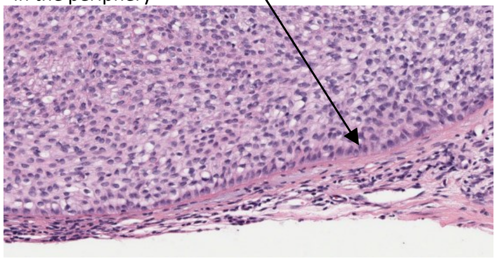
OTHER HIGH YIELD POINTS

- Communicates with the epidermis

Path Presenter



Pale to clear-staining cytoplasm, peripheral palisading of basaloid cells, and thickened pink basement membrane in the periphery



TRICHILEMMOMA

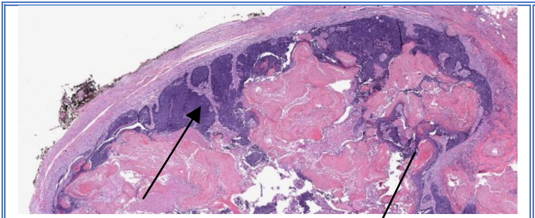
MORPHOLOGY

- Overall circumscribed looking lobular proliferation of **mature squamoid cells with pale to clear-staining cytoplasm, peripheral palisading of basaloid cells, and thickened pink basement membrane in the periphery**

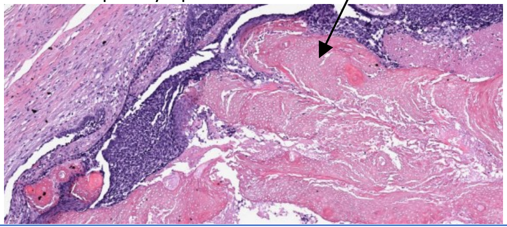
OTHER HIGH YIELD POINTS

- Almost exclusively on the face
- Multiple broad connections to epidermis and follicles
- Associated with Cowden’s Syndrome:
  - COWden’s Syndrome
  - PTEN mutation (tumor suppressor) on chromosome 10
  - Multiple hamartomas (mouth, GI tract)
  - Thyroid carcinoma (usually Follicular)
  - Breast Cancer (very high risk)
  - Endometrial Cancer
  - Macrocephaly
  - TrichileMMOOOOmas

Path Presenter



Basaloid peripheral matrical cells and “ghost cells” with abundant pink cytoplasm



PILOMATRICOMA (CALCIFYING EPITHELIOMA OF MALHERBE)

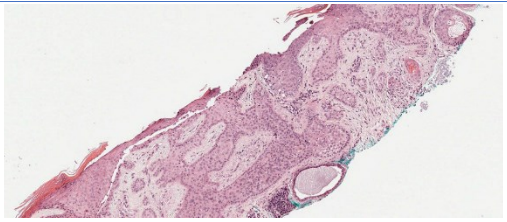
MORPHOLOGY

- Sharply circumscribed dermal mass with **basaloid peripheral matrical cells and “ghost cells” with abundant pink cytoplasm** and no nucleus

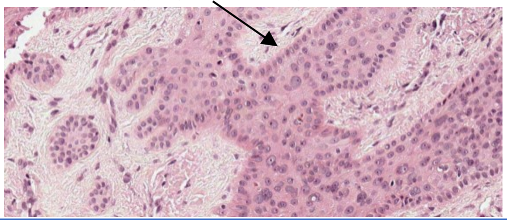
OTHER HIGH YIELD POINTS

- Benign tumor arising from hair matrix
- Usually, children and young adults in head, neck or upper extremities
- Dystrophic calcification is frequently seen
- Foreign-body giant cell reaction surrounding the tumor is common
- Aggressive pilomatrixoma: Benign tumor arising from hair matrix
- Infiltrative, prominent nucleoli, necrosis, mitoses, sarcomatoid features, transition to squamous -> Pilomatrical Carcinoma

Path Presenter



Reticulated cords and nests of pale pink staining, monotonous glycogen-containing cells



TUMOR OF FOLLICULAR INFUNDIBULUM

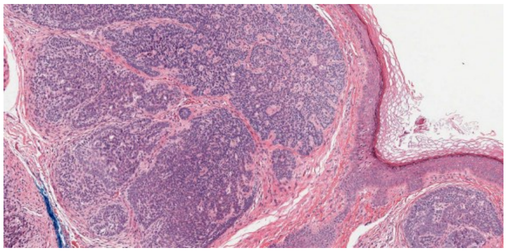
MORPHOLOGY

- **Acanthoma** composed of pale pink cells and sometimes clear cells
- The tumour forms **anastomosing narrow strands** that run parallel to the epidermis. These strands have **peripheral palisading of basaloid cells**
- Subepidermal tumor of **reticulated cords and nests of pale pink staining, monotonous glycogen containing cells**

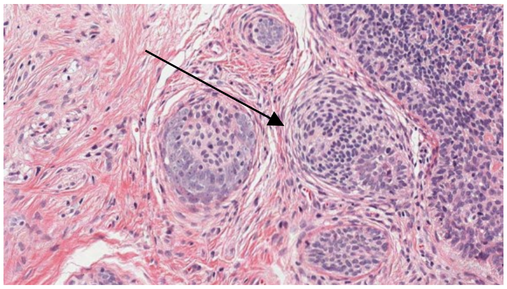
OTHER HIGH YIELD POINTS

- Arise in the head and neck, and clinically resemble superficial basal cell carcinoma
- Can mimic Fibroepithelioma of Pinkus (those are basaloid, these are pink)
- No significant atypia or pleomorphism

Path Presenter



Basaloid islands of cells with papillary mesenchymal bodies



TRICHOEPITHELIOMA

MORPHOLOGY

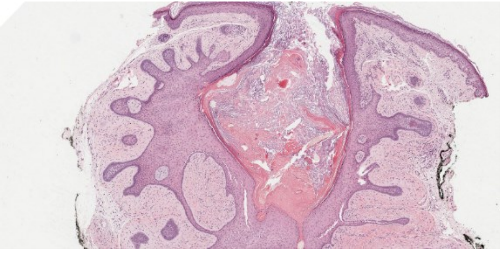
- Dermal tumor of **basaloid islands of cells** with fibroblastic looking stroma known as **papillary mesenchymal bodies**/rudimentary hair follicles (aggregates of abortive attempts to form papillary mesenchyme)

OTHER HIGH YIELD POINTS

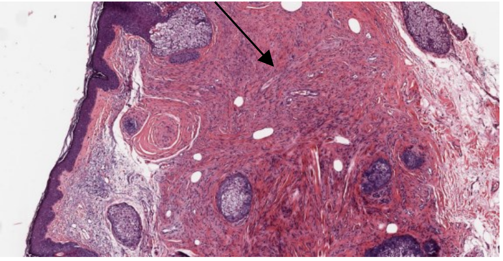
- Desmoplastic variant can look like microcystic adnexal carcinoma but as a papule with a central dell as opposed to MAC which is a plaque
- **Another mimic is infiltrative basal cell carcinoma**, but there is retraction and cellular atypia in basal cell carcinoma (IHC for BCL2 would be positive in BCCs and the basal layer of trichoepithelioma, and CD34 would be positive in the spindle-shaped cells around the basaloid islands of desmoplastic trichoepithelioma)
- Association with **Brooke Spiegler Syndrome**: Multiple cylindromas, trichoepitheliomas, spiradenomas, milia
- **Multiple familial trichoepitheliomas**: Multiple trichoepitheliomas only

Path Presenter

Radiating cords from a central follicular structure



Loose stroma with ground substance in trichodiscoma



FIBROFOLLICULOMA/TIRCHODISCOMA

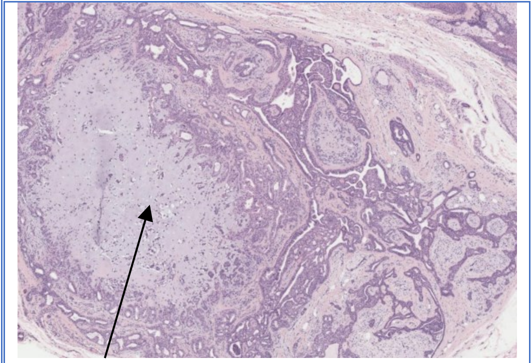
MORPHOLOGY

- **Radiating cords from a central follicular structure** with surrounding well-circumscribed proliferation of loose stroma and delicate spindle cells
- Trichodiscoma is on a spectrum from fibrofolliculoma, with the former consisting of just **loose stroma with mucin/ground substance**

OTHER HIGH YIELD POINTS

- Considered a hamartoma of hair follicle
- Multiple skin-colored papules
- Associated with **Birt-Hogg-Dubé syndrome**:
  - Autosomal dominant, mutation in the FLCN (BD) gene on chromosome 17p11.2 encoding folliculin protein
  - Cutaneous fibrofolliculomas, oncocytic neoplasm, and chromophobe renal cell carcinoma
  - Lung cysts and spontaneous pneumothorax

Path Presenter



Well circumscribed, mixture of epithelial cells embedded in myxoid, cartilaginous, or fibrous stroma

CHONDROID SYRINGOMA (CUTANEOUS MIXED TUMOR)

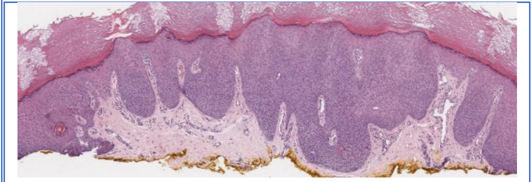
MORPHOLOGY

- Well circumscribed mixture of epithelial cells in **cords and nests with cartilaginous matrix** that varies depending on the degree of mesenchymal versus epithelial components

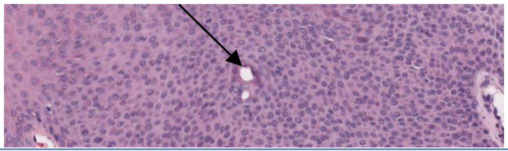
OTHER HIGH YIELD POINTS

- **Essentially a pleomorphic adenoma**, but primary to the skin
- Ducts of variable size and shape are lined by two layers of cuboidal cells and a peripheral layer of myoepithelial cells

Path Presenter



Downward growth of monotonous, evenly spaced cells with occasional duct formation



ECCRINE POROMA

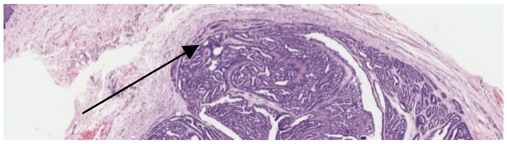
MORPHOLOGY

- Acanthotic lesion connecting to the epidermis that resembles an endophytic seborrheic keratosis (downward growth) with **monotonous, evenly spaced cells with occasional duct formation**

OTHER HIGH YIELD POINTS

- Duct formation will be EMA/CEA positive
- If purely intraepidermal -> hidroacanthoma simplex

Path Presenter



Arborizing network of cuboidal cells

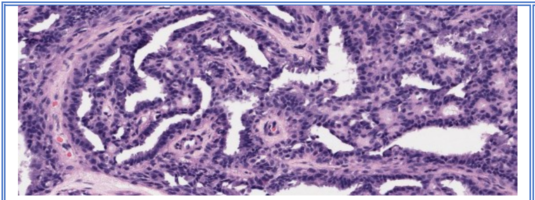
HIDRADENOMA PAPILLIFERUM

MORPHOLOGY

- Dermal papillary and **arborizing network of cuboidal cells** that connect to the epidermis

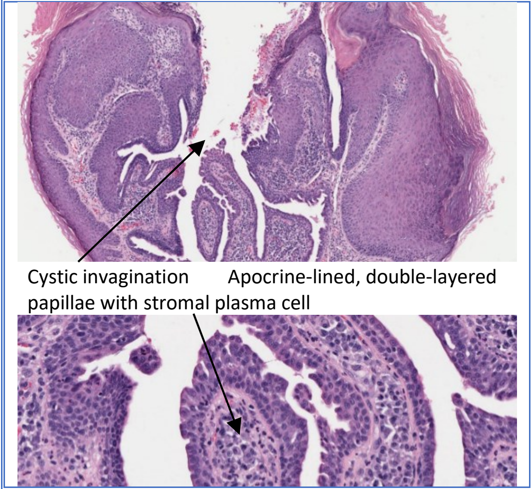
OTHER HIGH YIELD POINTS

- Solid, skin colored papule, usually < 1 - 2 cm
- Neoplasm of sweat glands in the vulva and perianal regions



- Usually solitary and <1cm in middle-aged females
- Partially cystic, glandular, and papillary areas
- IHC: CK7, EMA, CEA, GCDFP-15, ER, PR, androgen receptor

Path Presenter



Cystic invagination Apocrine-lined, double-layered papillae with stromal plasma cell

SYRINGOCYSTADENOMA PAPILLIFERUM

MORPHOLOGY

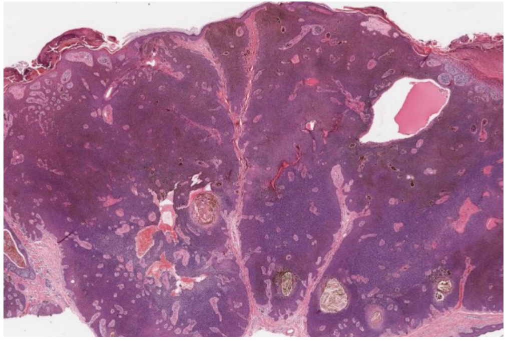
- **Cystic invagination** from the epithelium into the underlying dermis of **apocrine-lined, double-layered papillae with stromal plasma cells**
- Innermost layer is composed of columnar cells with decapitation secretion
- Outermost layer is composed of cuboidal cells with papillary projections

OTHER HIGH YIELD POINTS

- Benign, hamartomatous, adnexal tumor
- Most commonly occurring in the head and neck in early childhood
- **SCAP**: **S**calp location, **C**ommunicate**s** with the epidermis, **A**ssociated with Nevus Sebaceous (in 1/3 of cases), **P**lasma cells within papillae
- Looks similar to hidradenoma papilliferum but in the head and neck

Path Presenter

Monotonous cells that resemble poroma cells



ACROSPIROMA

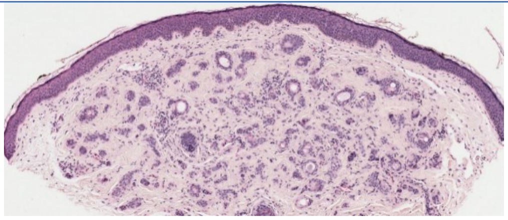
MORPHOLOGY

- Dermal tumor consisting of **monotonous cells that resemble poroma cells** but deeper down

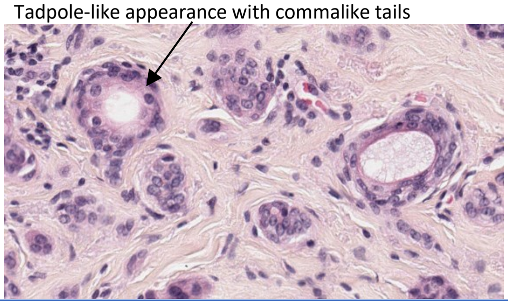
OTHER HIGH YIELD POINTS

- Include nodular hidradenoma and clear cell hidradenoma
- Evidence of ductal differentiation
- Pink squamous-looking cells or clear cell change can be present

Path Presenter



Tadpole-like appearance with commalike tails



SYRINGOMA

MORPHOLOGY

- Clinical: papule in cheek or lower eyelid
- Microscopic: Small ducts, nests, cords, and cysts in the superficial dermis lined by 1-2 layers of small, bland cuboidal cells that frequently have a **tadpole-like appearance with commalike tails (like paisley)**

OTHER HIGH YIELD POINTS

- Most common in the head/neck, especially eyelids
- Dilated ducts may contain eosinophilic contents
- Nests, cords, and cysts are EMA positive
- If deep/perineural invasion -> consider Microcystic Adnexal Carcinoma (MAC)

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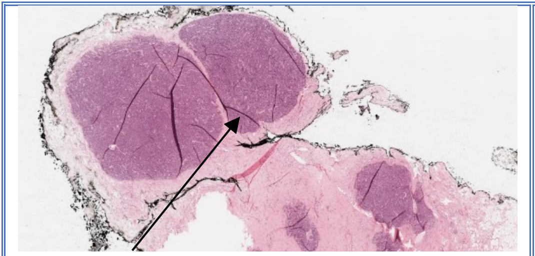
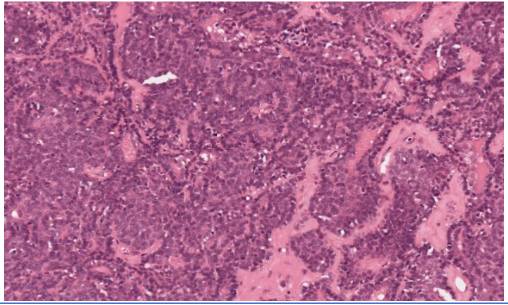


“Blue cannonballs” composed of 2 cell types:



SPIRADENOMA

MORPHOLOGY

- Dermal tumor consisting of **“blue cannonballs” or basophilic tumor nodules**

OTHER HIGH YIELD POINTS

- Tumor lobules may be partially encapsulated
- Biphasic appearance with **2 cell types:**
  - Peripheral small cells with scant cytoplasm and small hyperchromatic nuclei
  - Central larger cells with eosinophilic cytoplasm and oval, vesicular nuclei
- Stroma can have prominent vessels +/- hemorrhage
- Tumor lobules are sometimes surrounded by thickened basement membrane, similar to cylindroma
- Associated with Brooke Spiegler Syndrome
  - Mutations in CYLD gene on chromosome 16q12-q13
  - Multiple trichoepitheliomas, multiple cylindromas, sometimes spiradenoma or spiradenoma/cylindroma overlap lesions

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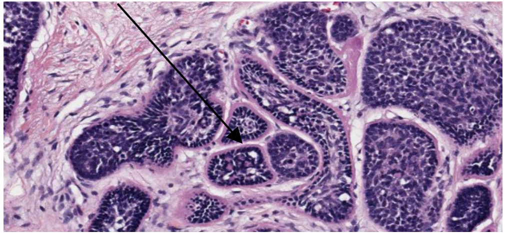
Basaloid nests with a “jigsaw puzzle” look and dense eosinophilic basement membrane surrounding each nest



CYLINDROMA

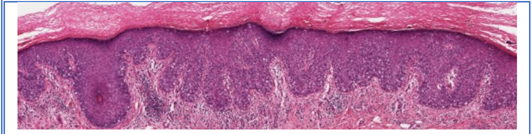
MORPHOLOGY

- Basaloid nests with a **“jigsaw puzzle”** look and **dense eosinophilic basement membrane surrounding each nest**

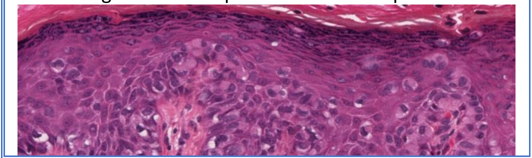
OTHER HIGH YIELD POINTS

- Tumor lobules have a complex pattern and can resemble spiradenoma but do not contain the two cell types of a spiradenoma

Path Presenter



Buckshot growth of neoplastic cells in the epidermis



EXTRAMAMMARY PAGET’S DISEASE (EMPD)

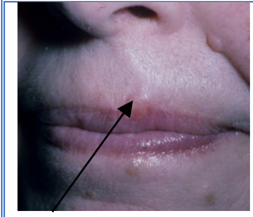
MORPHOLOGY

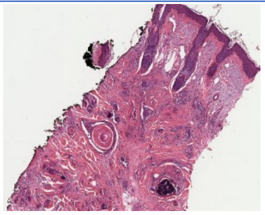
- **Buckshot growth of neoplastic cells in the epidermis**

OTHER HIGH YIELD POINTS

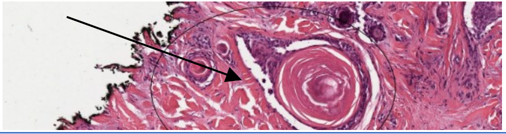
- Rarely with underlying dermal involvement
- Usually not right at the dermal-epidermal junction as opposed to melanoma
- IHC: CK7+/EMA+

Path Presenter





Plaque Comma-shaped ducts with keratin-filled cysts that infiltrate down to the subcutis



MICROCYSTIC ADNEXAL CARCINOMA

MORPHOLOGY

- Clinical: **plaque**
- Microscopic: **comma-shaped, dilated ducts** with keratin-filled cysts that **infiltrate down to the subcutis**

OTHER HIGH YIELD POINTS

- Resembles desmoplastic trichoepithelioma and syringoma histologically, but clinical appearance varies (plaque in MAC, papule in trichoepithelioma and syringoma)

Path Presenter

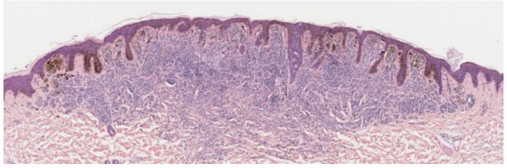
9. SKIN PATHOLOGY

MELANOCYTIC TUMORS

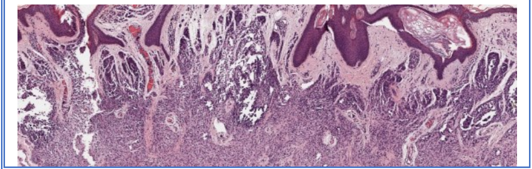
BENIGN AND MALIGNANT NEVI

- Nevi
- Spitz nevus
- Blue nevus
- Clark's dysplastic nevus
- Melanoma

Compound nevus with absent shoulder and normal maturation from top to bottom



Intradermal nevus



NEVI

MORPHOLOGY

- Common Types:
  - **Junctional nevus:** Nevus cells limited to the epidermis
  - **Compound nevus:** Few nests in the epidermis and dermis
  - **Intradermal nevus:** Dermal component only

OTHER HIGH YIELD POINTS

- Signs of a benign nevus: absence of a "shoulder" or junctional component extending past the dermal component and normal maturation or reduction in size and shape from the top to the bottom of the dermis

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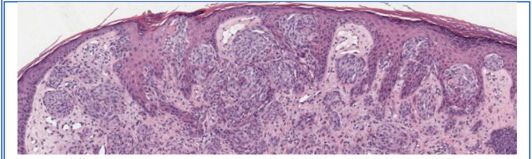
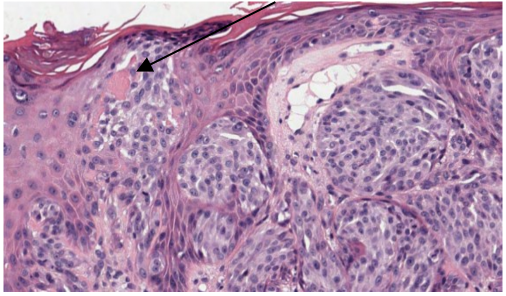


Epithelioid or spindled cells with epidermal hyperplasia and eosinophilic globules (Kamino bodies)



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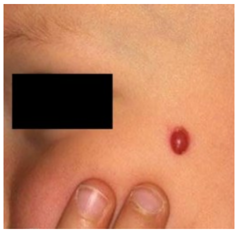
SPITZ NEVUS

MORPHOLOGY

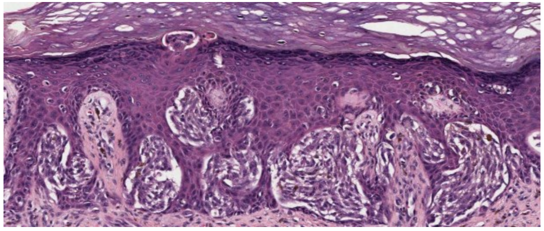
- Well-circumscribed nest of epithelioid or spindled cells with epidermal hyperplasia of the rete ridges and **no "shoulder"**
- Melanocytes are **large, spindled**, or epithelioid
- Junctional nests often show **separation artifacts (clefting)** to the surrounding epidermis and are **oriented perpendicularly to the epidermis**
- **Pagetoid** melanocytes centrally
- **PAS positive eosinophilic hyaline globules (Kamino bodies) at the DEJ**

OTHER HIGH YIELD POINTS

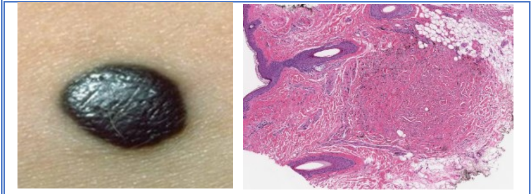
- Child or young adult with a pink smooth, dome-shaped firm papule or nodule on the face, trunk, or extremities
- Maturation of the dermal component



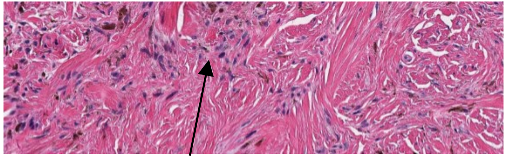
Pink, dome shaped papule



Vertically oriented nests of epithelioid and spindled cells



Blue/black papule. melanocytes with abundant melanin



Bipolar spindled dendritic melanocytes

BLUE NEVUS

MORPHOLOGY

- Clinical: **blue or black macule, papule, or nodule**
- Microscopic: **dermal melanocytes with abundant melanin**

OTHER HIGH YIELD POINTS

- Common blue nevus has **bipolar spindled dendritic melanocytes embedded in dense collagenous stroma,** whereas cellular blue nevus is composed of these cells plus ovoid cells with clear cytoplasm arranged in nests
- Lack high mitotic activity, marked cytologic atypia, or necrosis

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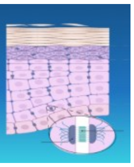

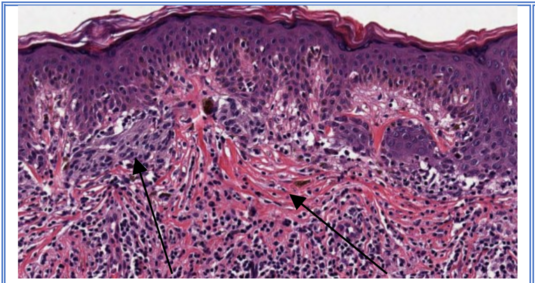

Fusion of adjacent nests and dermal lamellar fibroplasia

CLARK'S DYSPLASTIC NEVUS

MORPHOLOGY

- Melanocytes show nuclear enlargement and pleomorphism with **fusion of adjacent nests**, upward pagetoid spread, and **dermal lamellar fibroplasia** or darker, wavy stroma below nevus cells

OTHER HIGH YIELD POINTS

- Asymmetric distribution and/or shoulder present

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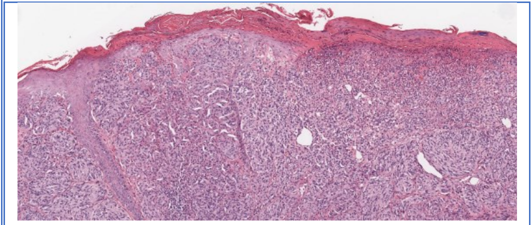
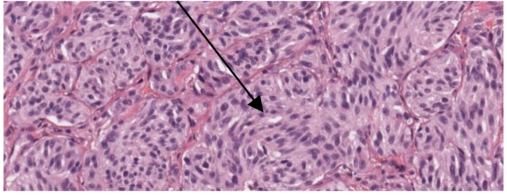
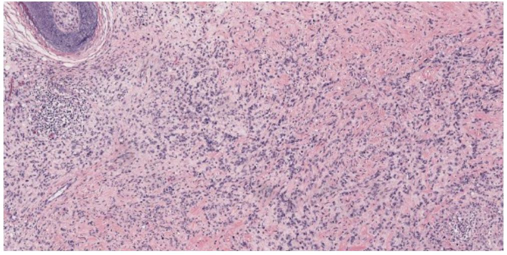


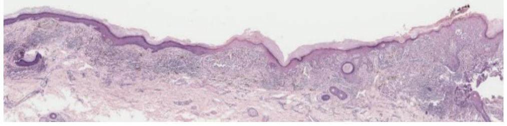
Ulcerated nodular type melanoma composed of cytologically atypical melanocytic nests



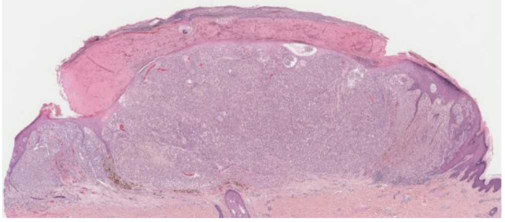
Desmoplastic type melanoma (below)



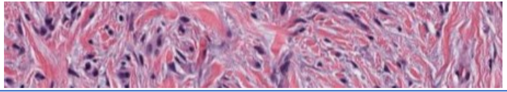
Malignant Melanoma, Superficial Spreading Type



Nodular Melanoma



Spindle cell Melanoma



MELANOMA

MORPHOLOGY

- Clinical: **ABCDE** (**A**symmetry, irregular **B**order, variegated **C**olor, **D**iameter >5 mm, **E**volving/changing)
- Microscopic: Asymmetric, poorly circumscribed lesion composed of **cytologically atypical melanocytic nests**. *The great mimicker – can mimic almost any malignancy in appearance cytologically
- IHC: S100 (nuclear and cytoplasmic), SOX10 (nuclear), MelanA / MART1 (cytoplasmic), HMB45 (cytoplasmic), Tyrosinase (cytoplasmic), MiTF (nuclear), PRAME (nuclear)

OTHER HIGH YIELD POINTS

- Accounts for the majority of skin cancer mortality
- Can occur de novo or in a pre-existing nevus
- Risk factors include high sun exposure, fair skin, personal or family history, increased number of nevi (particularly if dysplastic), germline mutations, immunosuppression
- Prognosis most dependent on Breslow depth
- In higher stage disease, BRAF mutation testing is recommended
- **Desmoplastic type**
  - Spindled cells not circumscribed, scar like, with lymphoid aggregates
  - Can look as bland as neurofibroma
  - May not retain melanocytic markers except SOX10 and S100
- **Other** types of Melanomas:
  - Malignant Melanoma**, Superficial Spreading** Type: Most common subtype, radial growth with pagetoid spread
  - Malignant Melanoma, **Lentigo Maligna** Type: Elderly patients on chronic sun damaged skin
  - **Nodular Melanoma**: Vertical growth phase
  - **Nevoid Melanoma**: Verrucous or doom shaped silhouette
  - **Acral Melanoma**: Acral location (palms, soles and subungual)
  - **Spindle Cell Melanoma**: Prominent spindle cell morphology
  - **Spitzoid Melanoma**: Mimics spitz nevus, with confluent growth pattern
  - **Melanoma Arising in Cellular Blue Nevus**: Presence of a pre-existing blue nevus at the periphery
  - **Melanoma Of Soft Parts**: Multilobulated lesion with nests and fascicles of oval to fusiform cells, separated by fibrous trabeculae
  - **Metastatic Melanoma**: Well-circumscribed nodule in the upper dermis with collarette formation, stromal fibrosis

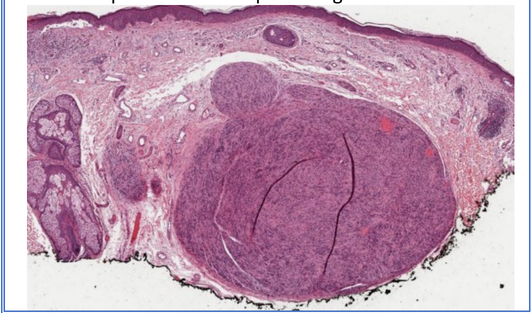
Path Presenter

9. SKIN PATHOLOGY

CUTANEOUS SOFT TISSUE TUMORS AND TUMORS OF HEMATOPOIETIC AND LYMPHOID ORIGIN

- Palisaded encapsulated neuroma
- Neurofibroma
- Granular cell tumor
- Neurothekeoma
- Hemangioma
- Glomus tumor
- Papillary endothelial hyperplasia (Masson's tumor)
- Kaposi sarcoma
- Angiosarcoma
- Atypical fibroxanthoma (AFX)
- Dermatofibroma (Benign fibrous histiocytoma)
- Dermatofibrosarcoma protuberans (DFSP)
- Fibrous hamartoma of infancy
- Fibroepithelial polyp (Acrochordon)
- Angiofibroma
- Sclerotic fibroma
- Scar
- Leiomyoma
- Mycosis fungoides
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma

Delicate spindle cells with palisading



PALISADED ENCAPSULATED NEUROMA

MORPHOLOGY

- Dermal nodule made up of **delicate spindle cells with palisading**

OTHER HIGH YIELD POINTS

- 90% on the face of elderly individual
- Not truly encapsulated and fascicles are separated by clefts
- IHC: S100 (+) and EMA (+) peripherally (around "capsule"), GFAP (-)

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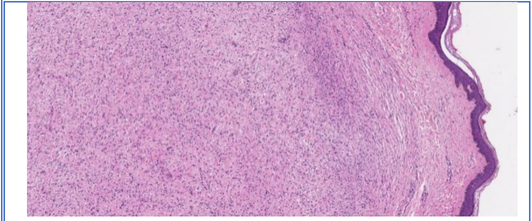
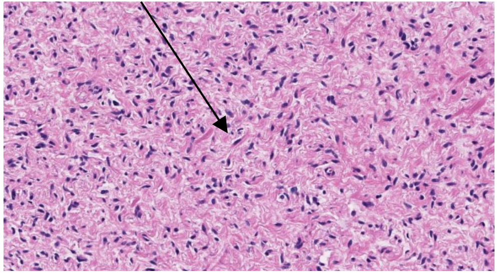


Delicate spindle cells in a sclerotic or mucinous stroma



NEUROFIBROMA

MORPHOLOGY

- Dermal lesion composed of **delicate spindle cells** (Schwann cells, fibroblasts, perineural-like cells, and residual nerve axons) **in a sclerotic or mucinous stroma**

OTHER HIGH YIELD POINTS

- Frequently multiple
- Sporadic in ~ 90% of cases; others are syndromic with NF1
- Loosely arranged spindle cells in haphazard arrangement
- Poorly defined cytoplasmic borders/processes–Small, hyperchromatic, wavy, or buckled nuclei
- IHC: S100(+) in ~ 50% of total cells (Schwann cells); CD34 (+)
- Admixed spindled fibroblasts; Neurofilament protein highlights intratumoral axons

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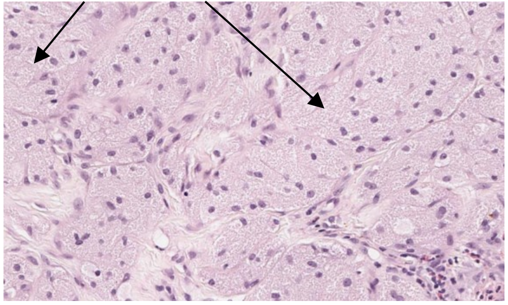
Abundant granular cytoplasm



GRANULAR CELL TUMOR

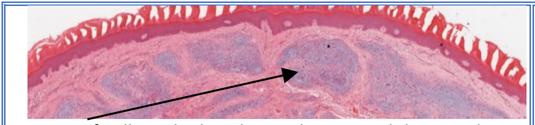
MORPHOLOGY

- Cells with **abundant granular cytoplasm and frequently overlying pseudoepitheliomatous hyperplasia** (epidermal change can mimic SCC)

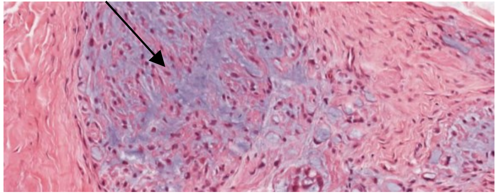
OTHER HIGH YIELD POINTS

- Benign tumor of putative schwannian origin
- IHC: PAS-D (+) granules; Strong, diffuse S100 (+), SOX10 (+), Calretinin (+), CD68 (+)

Path Presenter



Nests of cells with abundant pale eosinophilic cytoplasm in a myxomatous background



NEUROTHEKEOMA

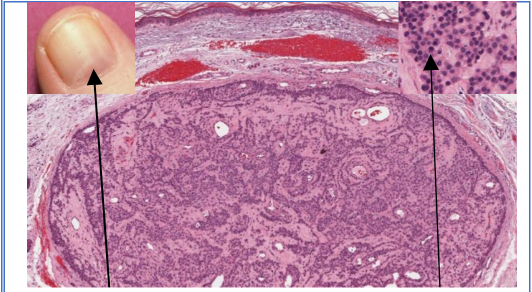
MORPHOLOGY

- Epithelioid to spindled cells **with abundant pale eosinophilic cytoplasm** arranged in multiple nests divided by **dense fibrous septa**
- **Myxoid variant** shows variable gray blue myxomatous change

OTHER HIGH YIELD POINTS

- Rare dermal tumor of uncertain histogenesis
- IHC: Often positive for variety of nonspecific markers, including NKI/C3, NSE, PGP9.5

Path Presenter



Red painful nodule (left upper inset) Round cells with central nuclei (right upper inset)

GLOMUS TUMOR

MORPHOLOGY

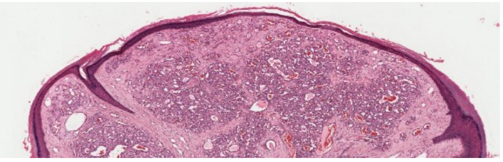
- Clinical: **small, red, painful nodule**
- Microscopy: Solid nests of **round cells with uniform, central nuclei** closely associated with variably sized blood vessels

OTHER HIGH YIELD POINTS

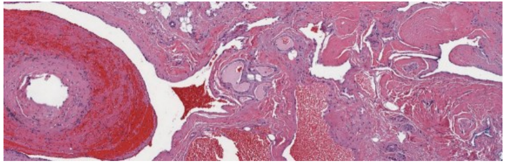
- Most common in distal extremities, particularly nail bed
- IHC: SMA (+)

Path Presenter

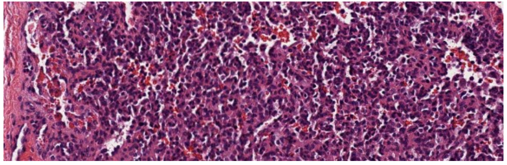
Pyogenic Granuloma



Cavernous Hemangioma



Infantile (Juvenile) Hemangioma



HEMANGIOMA

MORPHOLOGY

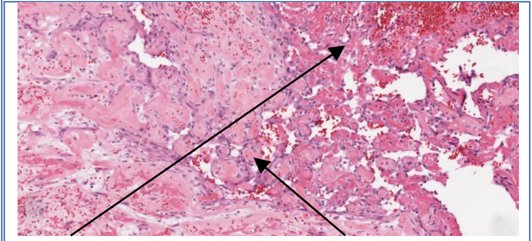
- Benign vascular tumors composed of blood vessels lined by plump to flattened endothelial cells with no atypia

OTHER HIGH YIELD POINTS

- **Lobular Capillary Hemangioma (Pyogenic Granuloma):** exophytic with collarette, numerous small capillaries radiating out from larger central vessels, may be ulcerated
- **Cavernous Hemangioma:** non-lobular, poorly demarcated proliferation of large cystically dilated vessels filled with blood
- **Infantile (Juvenile) Hemangioma:** tightly packed small to medium-sized vessels; onset during infancy with rapid growth and spontaneous involution, appearance changes over time; unique immunoprofile of placental vasculature with GLUT1 (+)

(From L to R: Pyogenic Granuloma, Cavernous Hemangioma, Infantile Hemangioma)

Link Link Link



Fibrin thrombus with associated papillary structures lined by a single layer of endothelium

PAPILLARY ENDOTHELIAL HYPERPLASIA (MASSON'S TUMOR)

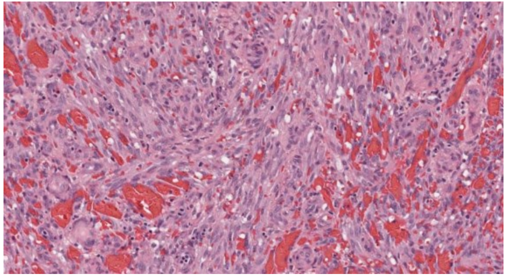
MORPHOLOGY

- Circumscribed, intravascular endothelial proliferation
- **Fibrin thrombus** with associated **papillary structures lined by a single layer of endothelium** that may form an anastomosing network

OTHER HIGH YIELD POINTS

- Reactive process

Jagged interconnected slit-like vascular channels and extravasated erythrocytes



KAPOSI SARCOMA

MORPHOLOGY

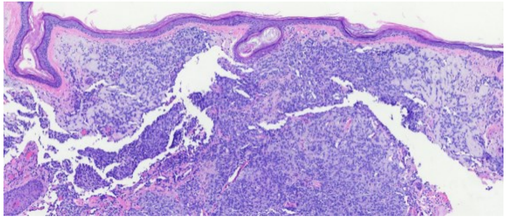
- Dermal spindle cell tumor with **jagged interconnected slit-like vascular channels and extravasated erythrocytes**
- "Promontory sign" of a blood vessel forming inside another blood vessel

OTHER HIGH YIELD POINTS

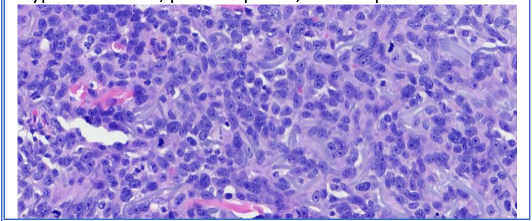
- Vascular neoplasm caused by HHV8
- Often AIDS-associated

Path Presenter

Infiltrative & poorly circumscribed malignant neoplasm



Hyperchromasia, pleomorphism, and frequent mitoses



ANGIOSARCOMA

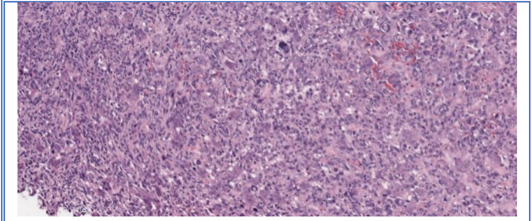
MORPHOLOGY

- **Infiltrative and poorly circumscribed malignant neoplasm** showing morphologic and/or immunophenotype evidence of vascular/endothelial differentiation

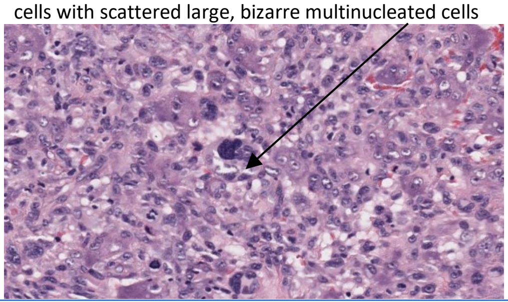
OTHER HIGH YIELD POINTS

- Most often scalp/face in elderly (sun-exposed) or breast s/p radiation
- Aggressive tumor treated surgically
- Variable vascular formation
- Often cytologic atypia (hyperchromasia, nuclear pleomorphism) and mitoses
- IHC: CD31 (+); CD34 (+); ERG (+); FLI1 (+); Epithelioid angiosarcomas may be CK (+)

Path Presenter



Dermal-based proliferation of spindled to epithelioid cells with scattered large, bizarre multinucleated cells



ATYPICAL FIBROXANTHOMA (AFX)

MORPHOLOGY

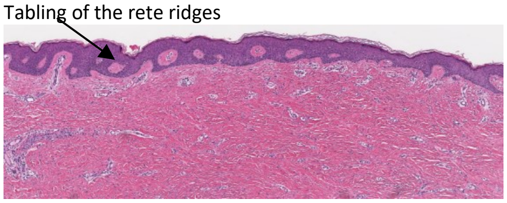
- Highly atypical and pleomorphic **dermal-based proliferation of spindled to epithelioid cells often with scattered large, bizarre multinucleated cells**

OTHER HIGH YIELD POINTS

- Mesenchymal neoplasm of no specific lineage of differentiation (can mimic a SCC or melanoma), usually H&N location
- Numerous mitoses, including atypical forms
- Diagnosis of exclusion:
  - Negative for melanocytic markers, cytokeratins (especially HMWCKs), p63, muscle (except for SMA), and vascular markers
  - Positive for nonspecific markers like CD10, CD68, CD99, and vimentin
- If it's unclear how deep it extends, should give a differential of dermal pleomorphic sarcoma

Path Presenter

Tabling of the rete ridges

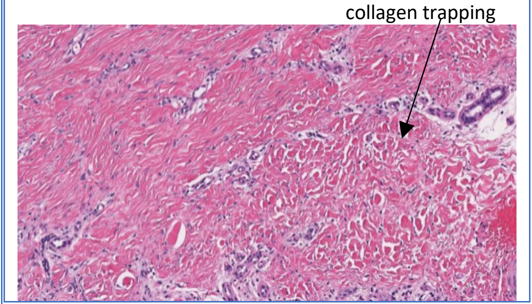


DERMATOFIBROMA (BENIGN FIBROUS HISTIOCYTOMA)

MORPHOLOGY

- Dermal-based proliferation of bland, spindled to histiocytoid-appearing cells with **collagen trapping at the periphery**
- Overlying epithelial basilar induction **("tabling" of the rete ridges)** with hyperpigmentation (may mimic BCC)

collagen trapping

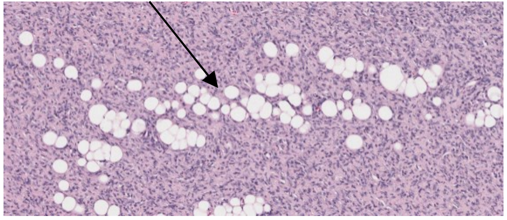


OTHER HIGH YIELD POINTS

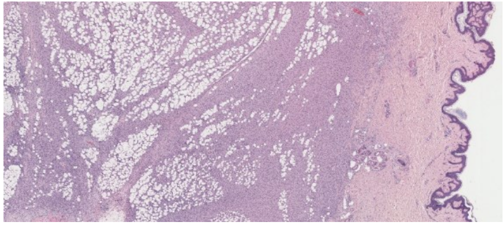
- Tumors are grossly circumscribed but microscopically have irregular, often jagged borders
- Evidence supports both neoplastic & reactive etiologies
- Many variants: Epithelioid, Cellular, with "monster cells"
- IHC: FXIIIA (+), CD163 (+), CD68 (+), CD34 (-)

Path Presenter

Honeycombing fat entrapment "pearls on a string"



Infiltrating the deep dermis and subcutis



DERMATOFIBROSARCOMA PROTUBERANS (DFSP)

MORPHOLOGY

- Dermal, cellular **spindle cell proliferation** of monomorphic cells in a **storiform or cartwheel arrangement infiltrating the deep dermis and subcutis**
- Subcutaneous areas typically show **honeycombing fat entrapment ("pearls on a string")**

OTHER HIGH YIELD POINTS

- Defined by t(17;22): Rearrangement of COL1A1 with PDGFB
- Lesional cells typically lack significant atypia and pleomorphism
- If loses storiform pattern -> herringbone pattern -> consider malignant transformation to fibrosarcoma
- IHC: Strong, diffuse CD34 (+), Factor XIIIA (-)

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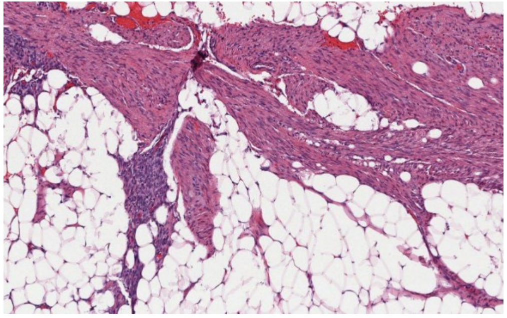
Mature fibrous tissue; round or spindled cells within loose stroma and interspersed mature fat



FIBROUS HAMARTOMA OF INFANCY

MORPHOLOGY

- 3 components:
  - **Intersecting bands of mature fibrous tissue**, comprising spindle-shaped myofibroblasts and fibroblasts
  - Nests of immature **round, ovoid, or spindled cells within loose stroma**
  - **Interspersed mature fat**

OTHER HIGH YIELD POINTS

- Benign superficial fibrous lesion occurring in the first 2 years of life

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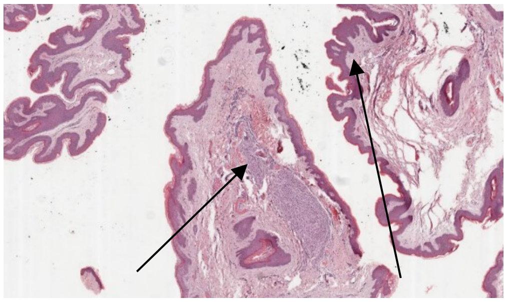


Mildly cellular fibrovascular core, hyperplastic or papillomatous epithelium

FIBROEPITHELIAL POLYP (ACROCHORDON)

MORPHOLOGY

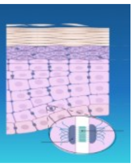
- Clinical: sessile or pedunculated skin-colored polyp
- Microscopic: **Mildly cellular fibrovascular core with loose stroma and abundant small vessels,** no adnexa, **and lined by hyperplastic or papillomatous epithelium**

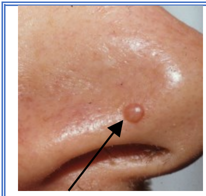
OTHER HIGH YIELD POINTS

- Common benign tumors often secondary to trauma
- No dysplasia

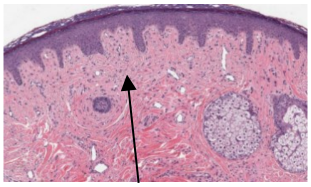
Path Presenter

9. SKIN PATHOLOGY

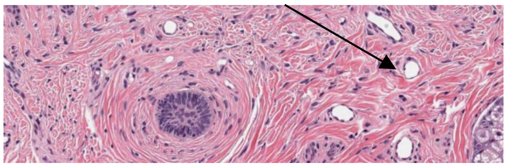




Dome-shaped papule



Spindled to stellate, and multinucleated fibroblasts in dense collagenous stroma with ectatic thin-walled blood vessels



FIBROUS PAPULE

MORPHOLOGY

- Clinical: solitary, dome-shaped flesh-colored papule on the nose or central face
- Microscopic: **Scattered bland, spindled to stellate, and multinucleated fibroblasts in dense collagenous stroma with ectatic thin-walled blood vessels**

OTHER HIGH YIELD POINTS

- Type of angiofibroma
- If enlarged, hyperchromatic nuclei with small nucleoli and scant amounts of eosinophilic cytoplasm -> consider pleomorphic fibroma

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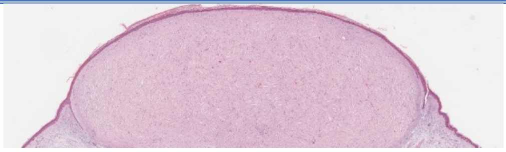
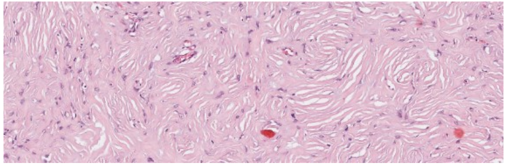


storiform/whorled pattern with prominent clefts



SCLEROTIC FIBROMA

MORPHOLOGY

- Circumscribed, unencapsulated dermal nodule composed of **thickened, hyaline-appearing collagen bundles in a storiform/whorled pattern with prominent clefts**

OTHER HIGH YIELD POINTS

- Sometimes an association with Cowden disease
- IHC: CD34 (+)

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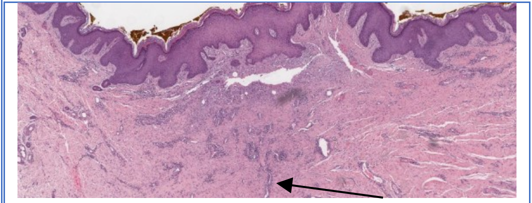
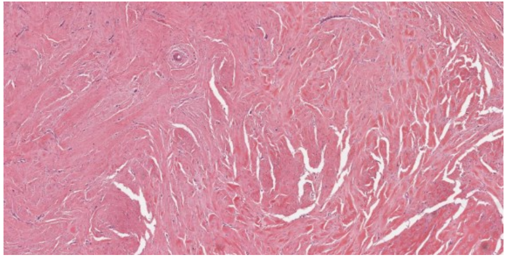


Scar with small, perpendicularly oriented vessels



Keloid with thickened, hyalinized collagen

SCAR

MORPHOLOGY

- Scar:
  - **Dense** collagen fibers that run parallel to the surface
  - **Small, perpendicularly oriented vessels**
  - Loss of adnexal structures
- Keloid
  - Dense proliferation of **thickened, hyalinized collagen** bundles
  - Decreased vessels compared to conventional and hypertrophic scars

OTHER HIGH YIELD POINTS

- Keloidal collagen can appear edematous due to increased dermal mucosubstances
- IHC: SMA (+)

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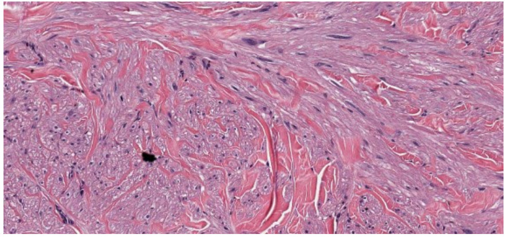
Pilar leiomyoma -fascicles dissecting between collagen

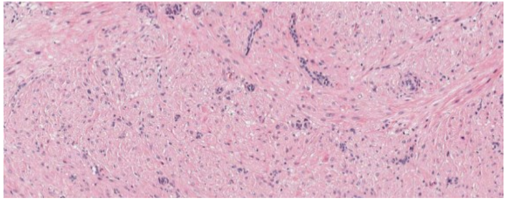


LEIOMYOMA

MORPHOLOGY

- Pilar leiomyoma:
  - Ill-defined dermal nodule composed of haphazardly arranged smooth muscle bundles/fascicles
  - **Fascicles often dissect between dermal collagen**
- Angioleiomyoma
  - Well-circumscribed neoplasm composed of mature smooth muscle cells arranged around prominent blood vessels

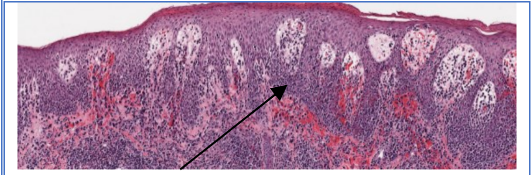
Angioleiomyoma



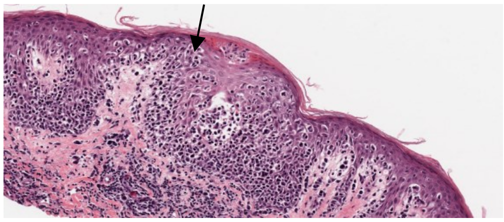
OTHER HIGH YIELD POINTS

- Benign smooth muscle tumor that is often painful (especially pilar type)
- If there are numerous mitoses, diffuse/marked cytologic atypia, or necrosis -> consider leiomyosarcoma

Path Presenter



Lymphocytes lining up at the dermal-epidermal junction with a Pautrier's microabscess



MYCOSIS FUNGOIDES

MORPHOLOGY

- Atypical lymphoid infiltrate with epidermotropism or lymphocytes in the epidermis without spongiosis as well as **lymphocytes lining up like "birds on a wire" at the dermal epidermal junction**
- **Pautrier's microabscess** or solid intraepidermal nodule made up of malignant lymphocytes
- Morphology varies depending on the stage of tumor (patch, plaque, tumor)

OTHER HIGH YIELD POINTS

- Patch stage shows irregular patches in sun-protected sites
- Neoplastic cells are CD4+ T-lymphocytes, clonal TCR gene rearrangement

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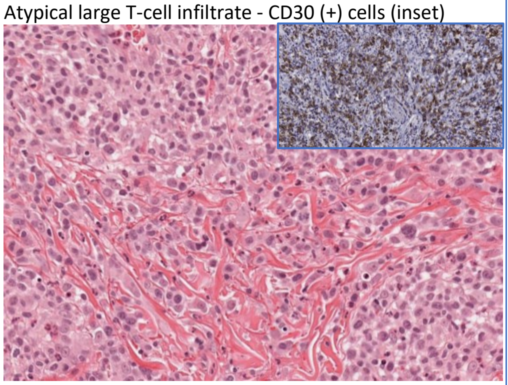
Atypical large T-cell infiltrate - CD30 (+) cells (inset)



LYMPHOMATOID PAPULOSIS (LyP)

MORPHOLOGY

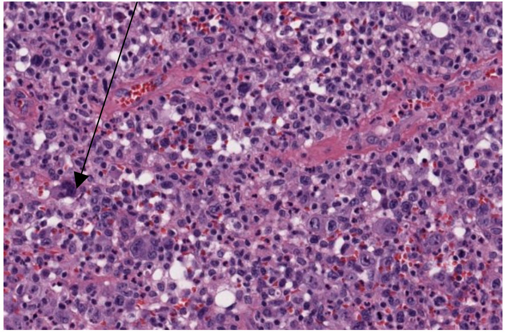
- **Wedge-shaped atypical large CD30 (+) T-cell infiltrate**
- Multiple variants with different morphology and immunoprofiles that can mimic other entities such as mycosis fungoides and anaplastic large cell lymphoma

OTHER HIGH YIELD POINTS

- Crops of papules and nodules usually at different stages of development
- Difference between this and mycosis fungoides is the clinical -> if lesions appear and spontaneously regress after weeks or months, consider LyP

Path Presenter

Large anaplastic cells with round, oval, or indented nuclei



PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA (ALCL)

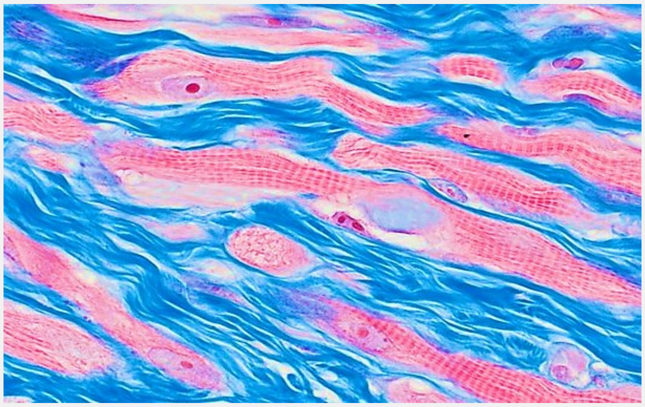
MORPHOLOGY

- Confluent sheet of **large anaplastic cells with round, oval, or indented nuclei**

OTHER HIGH YIELD POINTS

- Solitary or localized papules or masses
- >75% malignant cells positive for CD30
- Unlike primary systemic ALCL, cutaneous ALCL is usually ALK (-) -> if positive, consider cutaneous spread of primary systemic ALCL

Path Presenter

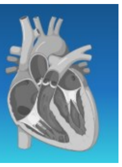


Masson's trichrome stain highlighting cross-striations in a paratesticular rhabdomyoma (sclerosing variant). Image courtesy: Susan Prendeville, MD

CHAPTER 10: CARDIOVASCULAR PATHOLOGY

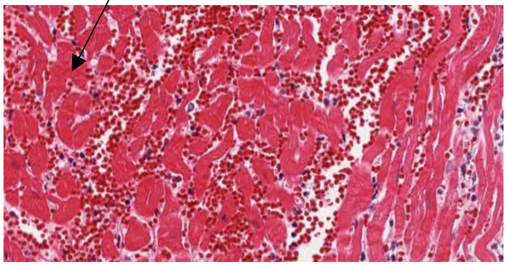
Upasana Joneja, MD
Snehal Sonawane, MD
Naomi Hardy, MD
Akanksha Gupta, MD
Jared T. Ahrendsen, MD, PhD

10. CARDIOVASCULAR PATHOLOGY

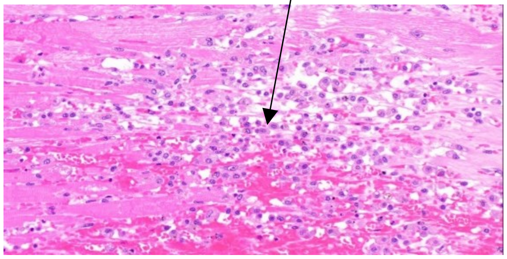


MYOCARDIAL DISORDERS

Hypereosinophilic cardiomyocytes (0-2 days)

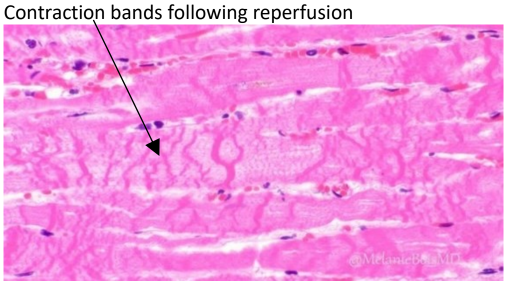


5-7 days infarct, collection of neutrophils & macrophages



Credit: Melanie Bois MD @MelanieBoisMD

Contraction bands following reperfusion



Credit: Melanie Bois MD @MelanieBoisMD

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MYOCARDIAL INFARCTION

MORPHOLOGY

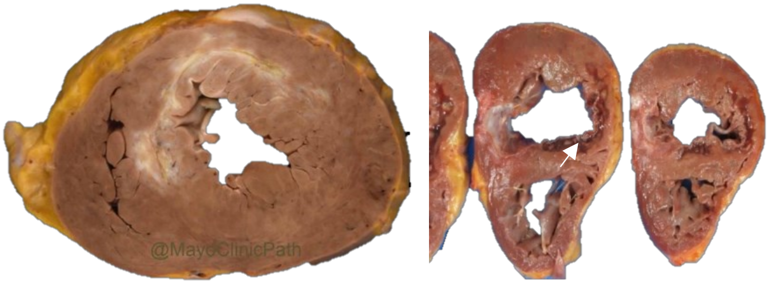
- Coagulative necrosis & inflammation → granulation tissue → resorption of necrotic debris → organization and scar → reperfusion → contraction bands

TIMING OF PATHOLOGIC FINDINGS

- **0-2 days** (hyperacute) – hypereosinophilic myocytes
- **<5 days** (acute) – mostly neutrophilic inflammation and coagulative necrosis; grossly: pale yellow
- **~1 week** (subacute) – granulation tissue and fibrosis; grossly: pale with hyperemic border
- **~1-3 months** (chronic) – dense fibrous scar

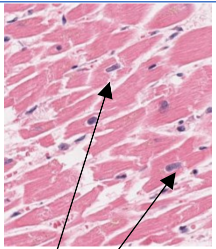
OTHER HIGH YIELD POINTS

- Myocardial infarction (MI): Ischemia leading to irreversible damage to the myocardium; most fatal MI are transmural
- **Sub-endocardium is affected first** (arteries are in the epicardium)
- Potential complications: death (most commonly due to arrhythmia), ventricular wall rupture (peak occurrence time: 3-7 days after MI), papillary wall rupture, ventricular aneurysm, mural thrombus, pericardial syndrome (Dressler syndrome), and heart failure
- **Reperfusion** – angioplasty or thrombolytic therapy dissolves thrombus and increases hemorrhage in the heart (contraction bands)

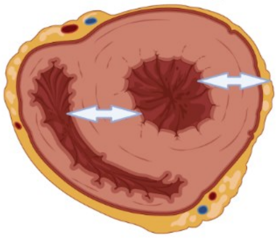


A. LAD-territory infarct (fibrous scar) Credit: Melanie Bois MD @MelanieBoisMD

B. Acute Anteroseptal infarct (Image credits: Remi MH, MD)



Box-car nuclei



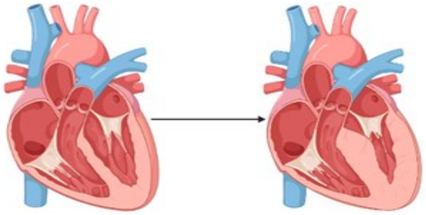
VENTRICULAR HYPERTROPHY

MORPHOLOGY

- Gross: **concentric left ventricular hypertrophy**
- Myocyte hypertrophy with rectangular, hyperchromatic nuclei often referred to as **"box-car"** nuclei

OTHER HIGH YIELD POINTS

- **Secondary to long-standing systemic hypertension**
- Exclude valvular and myocardial diseases
- In pulmonary hypertension, right ventricular hypertrophy occurs



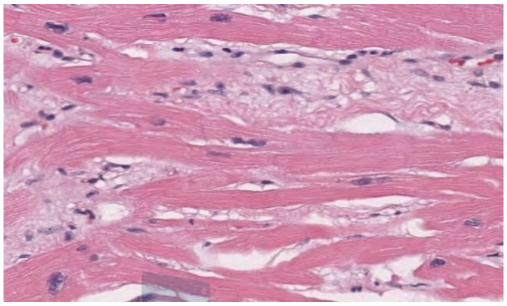
Normal heart Thickened septum

HYPERTROPHIC CARDIOMYOPATHY

MORPHOLOGY

- Gross: enlarged with **thickening of the ventricular walls, particularly the interventricular septum**
- Myocyte hypertrophy, myofiber disarray, and interstitial fibrosis

Link

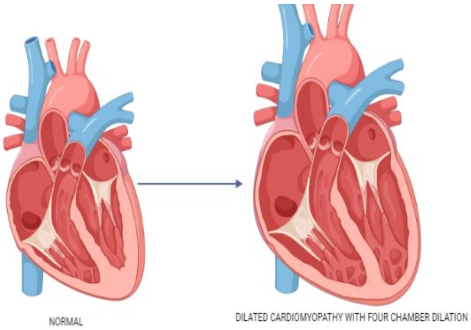


Disarray of fascicles, myocytes, and sarcomeres

OTHER HIGH YIELD POINTS

- Relatively common cause of **sudden cardiac death**, particularly in **young adults** with exertion
- Frequently have **mutations of sarcomere proteins**; often **autosomal dominant with incomplete penetrance** (~1/500 people)
- Can lead to outflow obstruction (hypertrophic obstructive cardiomyopathy, HOCM) and/or arrhythmia

Path Presenter



Created with BioRender.com

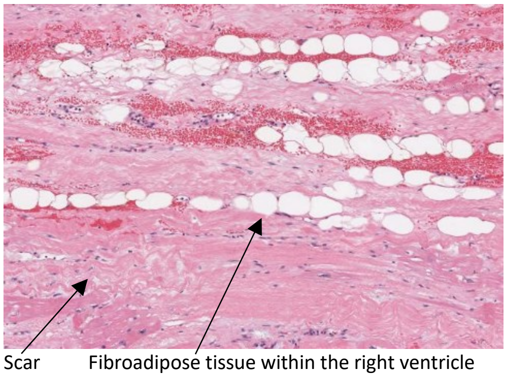
DILATED CARDIOMYOPATHY

MORPHOLOGY

- Gross: **left ventricular dilation >4cm**, dilated atria, normal to mildly thickened walls
- Non-specific; endomysial fibrosis and variation in fiber size

OTHER HIGH YIELD POINTS

- Four-chamber dilatation (**ventricles > atria**) in the absence of significant valvular, ischemic, or hypertensive disease
- Primary (multiple genes implicated) or secondary (post-inflammatory, peri/postpartum, endocrine, nutritional, alcohol, drugs/medications)
- **Adriamycin-associated cardiomyopathy**: grading scheme based on cardiomyocyte vacuolization and myofibrillar loss



Scar Fibroadipose tissue within the right ventricle

ARRHYTHMOGENIC CARDIOMYOPATHY

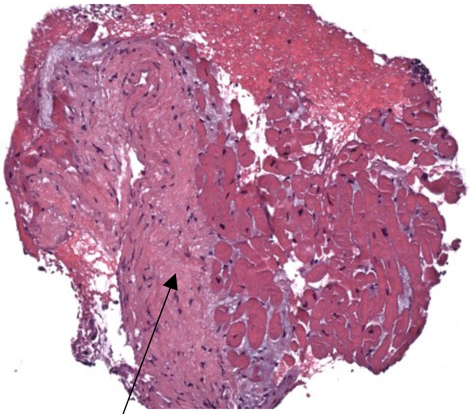
MORPHOLOGY

- Microscopic: **right ventricle infiltrated by fat and scar with aneurysm formation**

OTHER HIGH YIELD POINTS

- Also called arrhythmogenic right ventricular dysplasia
- Can lead to arrhythmias and conduction disturbances
- Both ventricles are often involved; **multiple genes in desmosomal protein-encoding genes are implicated** (familial)

Path Presenter



Endomyocardial fibrosis

RESTRICTIVE CARDIOMYOPATHY

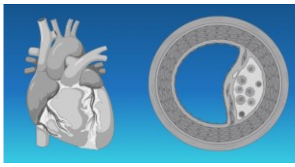
MORPHOLOGY

- Gross (variable depending on the cause): bilateral atrial dilatation, **thickened opaque endocardium, thickened valves**

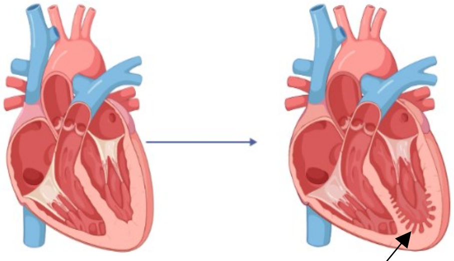
OTHER HIGH YIELD POINTS

- Causes: **endomyocardial fibrosis (common cause worldwide**), infiltrative heart disease (amyloidosis, hereditary hemochromatosis, radiation, sarcoidosis), idiopathic
- **Diastolic dysfunction with impaired relaxation** (must be distinguished from constriction)

Path Presenter



10. CARDIOVASCULAR PATHOLOGY



Created with BioRender.com

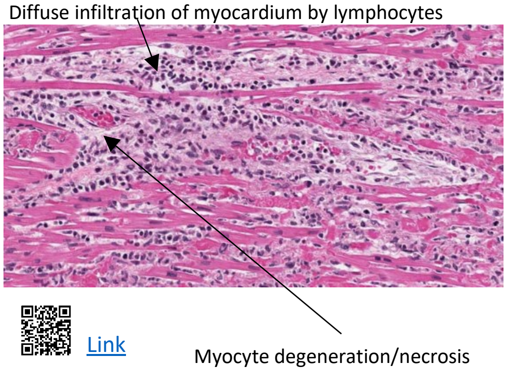
LEFT VENTRICULAR NONCONTRACTION

MORPHOLOGY

- Gross: prominent ventricular trabeculations, deep trabecular recesses, and a thin compacted layer, mostly involving the left ventricle

OTHER HIGH YIELD POINTS

- Most common in **infants/children**
- Associated with other congenital heart problems
- Can lead to heart failure, arrhythmias, and embolic events


Diffuse infiltration of myocardium by lymphocytes
Myocyte degeneration/necrosis

Link

MYOCARDITIS

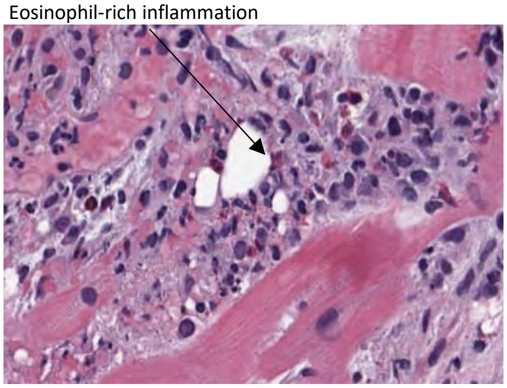
LYMPHOCYTIC MYOCARDITIS

MORPHOLOGY

- **Diffuse infiltration of myocardium by T-cells**, myocyte degeneration/necrosis

OTHER HIGH YIELD POINTS

- Most common form of myocarditis; usually children or young adults; diagnosis often made based on clinical findings
- Attributed to viruses (**coxsackievirus & adenovirus** most common)
- Most patients **respond to anti-inflammatory medication**, but a subset progress to dilated cardiomyopathy



EOSINOPHILIC MYOCARDITIS

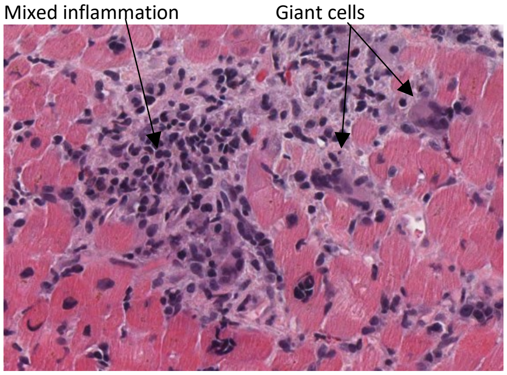
MORPHOLOGY

- **Eosinophil-rich inflammation** admixed with lymphocytes and histiocytes, commonly in a perivascular location

OTHER HIGH YIELD POINTS

- Often **allergic/hypersensitivity-associated**, rarely parasites
- Minimal damage
- Usually attributed to **medications**

Path Presenter



Link

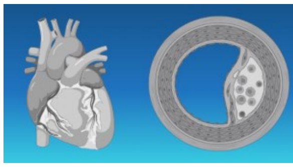
GIANT CELL MYOCARDITIS

MORPHOLOGY

- Microscopic: diffuse infiltration of the myocardium by a mix of **giant cells, lymphocytes, eosinophils, occasional neutrophils, and diffuse necrosis**

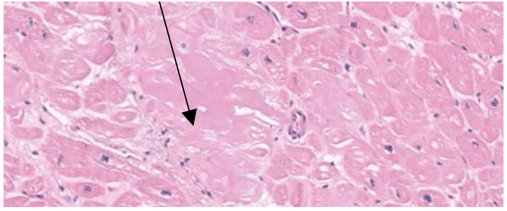
OTHER HIGH YIELD POINTS

- Also called **Fiedler's Disease**; rare, idiopathic, autoimmune
- Young adults with a rapidly deteriorating course (can be an indication for transplantation)
- **Differential diagnosis**: sarcoidosis (well-formed granulomas, not just giant cells), hypersensitivity myocarditis (may have giant cells and eosinophils but less necrosis and associated with the history of drugs, commonly methyldopa)

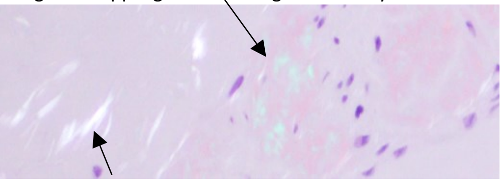


10. CARDIOVASCULAR PATHOLOGY

Amorphous acellular eosinophilic material



Congo red: apple green birefringence of amyloid



Pitfall: Collagen can also polarize (white)

[Link](#)

AMYLOIDOSIS

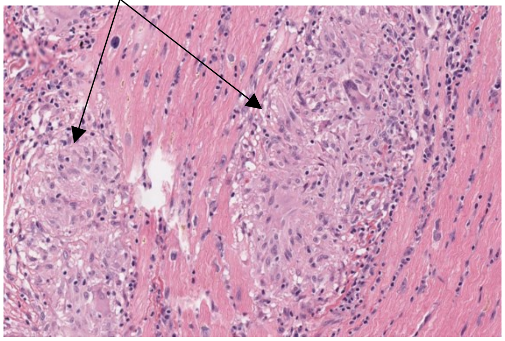
MORPHOLOGY

- Gross: large, firm, rubbery, or waxy heart
- Deposition of amorphous acellular eosinophilic material
- Congo Red stain shows "**Apple Green**" birefringence; a grey appearance on trichrome stain

OTHER HIGH YIELD POINTS

- **10 nm non-branching extracellular fibrils on electron microscopy**
- Can lead to restrictive cardiomyopathy, arrhythmias, conduction disturbances, and/or chronic heart failure
- Three main types: **AL (associated with plasma cell dyscrasia), AT (transthyretin: genetic mutation or senile), and AA (chronic inflammatory diseases, rare in the heart)**
- Subtyping with mass spectrometry or immunofluorescence
- Inflammatory cells and macrophages may be seen in the background

Well-formed granulomas



CARDIAC SARCOIDOSIS

MORPHOLOGY

- Well-formed, **"hard" granulomas** with fibrosis; may have some associated lymphocytic inflammation

OTHER HIGH YIELD POINTS

- Most have systemic involvement
- Sequalae: **interrupted conduction → heart block & arrhythmias → sudden death**

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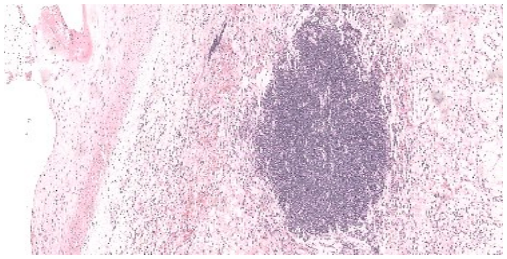
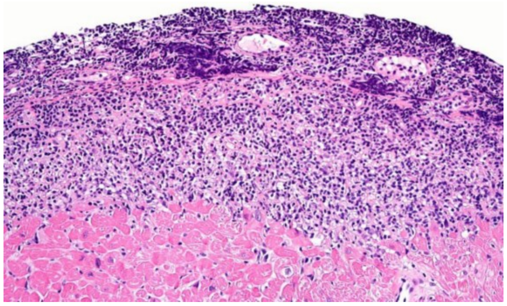
TRANSPLANT PATHOLOGY

Nodular endocardial lymphocytic inflammation





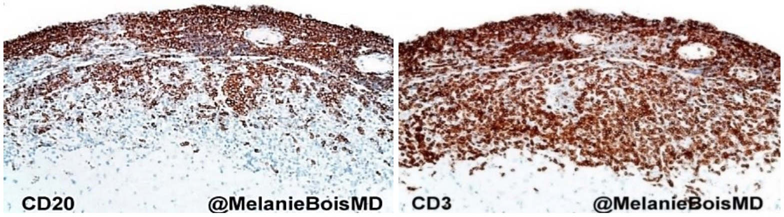
QUILTY LESION

MORPHOLOGY

- Nodular **endocardial lymphocytic inflammation**; **predominantly T lymphocytes** with admixed B cells and dendritic cells
- IHC: admixed CD3/CD5(+) T cells with PAX5/CD20(+) B cells and CD21(+) dendritic cells

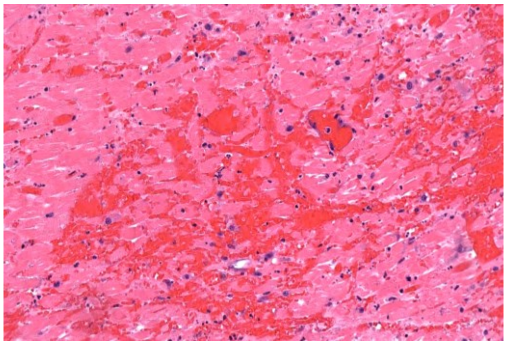
OTHER HIGH YIELD POINTS

- Seen in ~10-20% of transplant biopsies
- **This is not rejection** but weakly associated with rejection
- Differential diagnosis: Rejection (T-cell mediated)



[Link](#)

Credit: Melanie Bois MD @MelanieBoisMD



Hemorrhage (extensive)

HYPERACUTE REJECTION

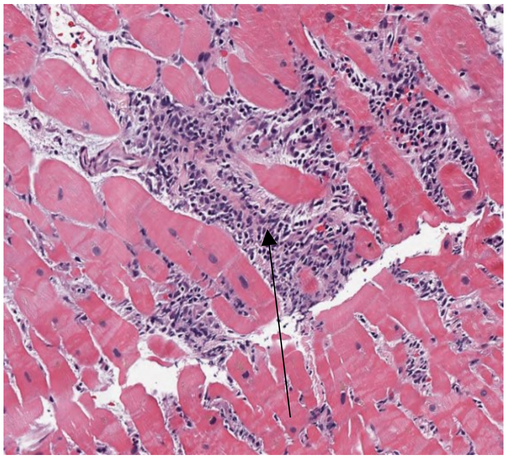
MORPHOLOGY

- Microscopic: **hemorrhage, edema, and platelet aggregates in blood vessels**
- Over time, neutrophils are seen

OTHER HIGH YIELD POINTS

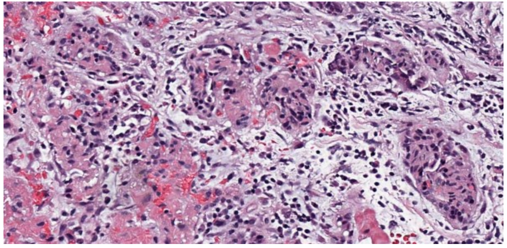
- **Develops immediately** or hours after transplantation and results in graft failure

Path Presenter

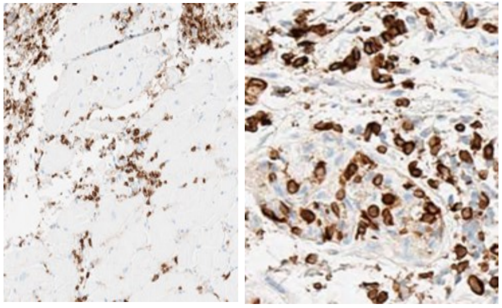


Transplant patient with lymphocytes in the muscle with myocyte damage

Perivascular lymphocytes



Lymphocytes are CD3(+) T cell



ACUTE CELLULAR REJECTION

MORPHOLOGY

- Infiltration by **T lymphocytes with myocyte damage** (must be **within the muscle or in a perivascular location**)
- IHC panel to further evaluate rejection: CD3, CD4, CD8, CD20, CD68
    - ➢ **Infiltrate composed of CD3+ T cells (both CD4+ and CD8+) with occasional CD68+ macrophages**

OTHER HIGH YIELD POINTS

- Usually **weeks to months after transplantation**, but can occur years after if insufficiently immunosuppressed
- May be asymptomatic or present with graft dysfunction

DIFFERENTIAL DIAGNOSIS

- **Quilty effect:** admixed B cells with CD21+ dendritic cells
- **Ischemic changes:** mostly PMNs and histiocytes (few lymphocytes)
- **Biopsy site:** mostly macrophages with B and T cells and disorganized myocytes with scarring
- **Post-transplant lymphoproliferative disorder:** mostly B cells
- **Infection:** a mixture of T and B cells
- **Eosinophils:** infection or drug effect

ISHLT GRADING SYSTEM	
0R (none)	No infiltrates or necrosis (no rejection)
1R (mild)	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
2R (Moderate)	Two or more foci of infiltrate with associated myocyte damage
3R (Severe)	Diffuse infiltrate with multifocal myocyte damage, ± edema, ± hemorrhage, ± vasculitis

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ANTIBODY-MEDIATED REJECTION (AMR)

MORPHOLOGY

- **Intravascular mononuclear cells** with accumulation in capillaries and small venules
- IHC: **positive for immunoglobulins, complement, and CD68 staining for macrophages**

OTHER HIGH YIELD POINTS

- Diagnosis based on clinical graft dysfunction, histologic evidence of capillary injury, immunopathologic evidence of AMR (IgG, IgM, IgA, C3d, C4d or C1q or CD68), and/or serologic evidence of anti-HLA or anti-donor antibodies

Grade	Definition	Findings
pAMR 0	Negative for pathologic AMR	Both histologic and immunopathologic studies are negative
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings present and immunopathologic findings are negative
pAMR 1 (I+)	Immunopathologic AMR alone	Histological findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+)
pAMR 2	Pathologic AMR	Both histological and immunopathologic findings are present
pAMR 3	Severe pathologic AMR	Rare. Histologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrate, endothelial cell pyknosis, and/or karyorrhexis and marked edema and immunopathologic findings are present. Poor outcome

PMID: 24263017

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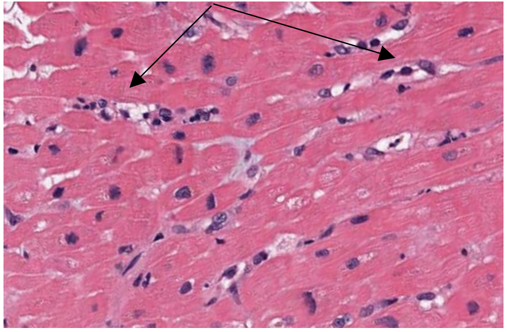
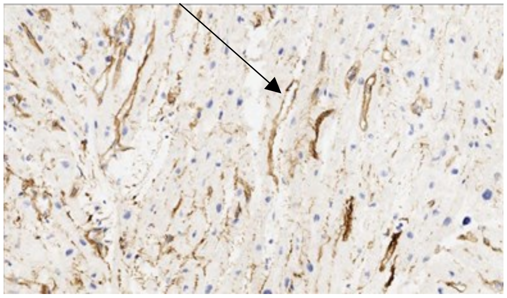
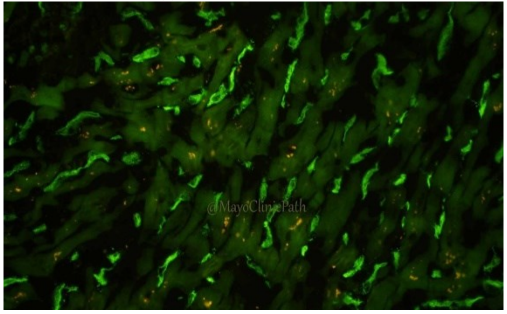
Intravascular chronic inflammation in capillaries



C4d+ capillary staining



C4d+ immunofluorescence staining Credit: Div. of Anatomic Pathology, Mayo Clinic



ALLOGRAFT VASCULOPATHY

MORPHOLOGY

- **Concentric, diffuse, vessel wall thickening** (and luminal narrowing) by intimal fibromuscular hyperplasia and mild chronic inflammation
- **Internal elastic lamina intact**
- Inflammation involves all layers of the vessel

OTHER HIGH YIELD POINTS

- Mainly impacts **arteries** (only seen at autopsy/explant)
- Can lead to thrombosis and/or chronic ischemia or infarction with fibrosis
- The main limitation to the long-term success of transplantation

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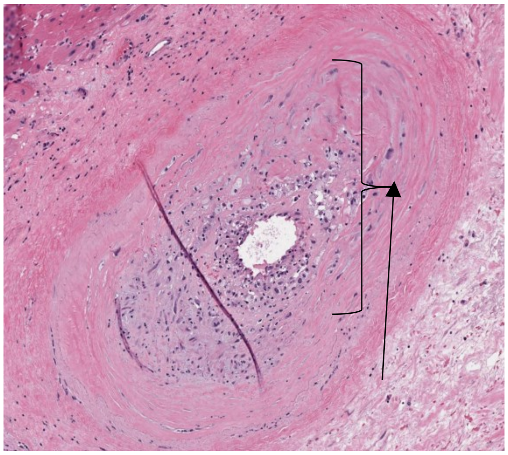
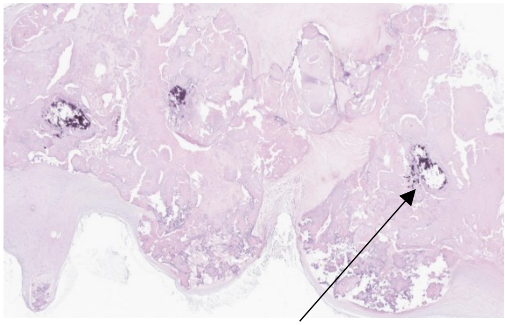


Concentric intimal fibromuscular hyperplasia

10. CARDIOVASCULAR PATHOLOGY

VALVULAR DISORDERS



Degenerative nodular calcifications

DEGENERATIVE VALVE DISEASE

MORPHOLOGY

- Fibrotic thickening, **nodular calcifications**, ± chronic inflammation

OTHER HIGH YIELD POINTS

- Usually affects the aortic valve and mitral annulus (left-sided)
- Clinically presents with stenosis ± insufficiency
- Common in **bicuspid valves**
- Treat with valve replacement

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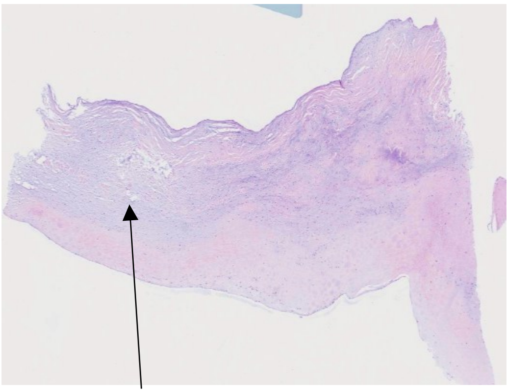

Central layer collagen (pink) replaced by mucopolysaccharides (gray-blue)

MYXOMATOUS/MYXOID DEGENERATION

MORPHOLOGY

- Gross: **floppy, translucent leaflets**
- Replacement of collagen with **mucopolysaccharides, particularly in the central spongiosa layer**

OTHER HIGH YIELD POINTS

- Impacts **mitral valve and aortic valve** (left-sided)
- Causes mitral valve prolapse (MVP), insufficiency, and regurgitation
- Aortic myxoid degeneration is often associated with/secondary to dilated aortic root
- Unclear etiology, genetics, and pathogenesis.
- MVP is seen in F > M

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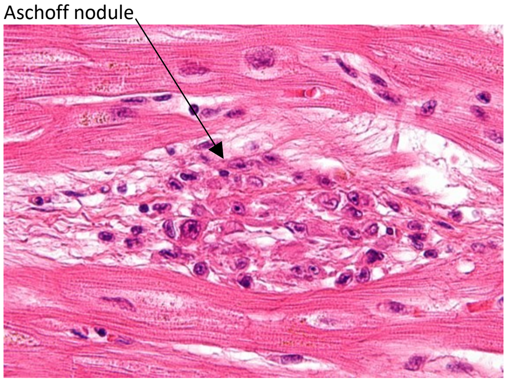
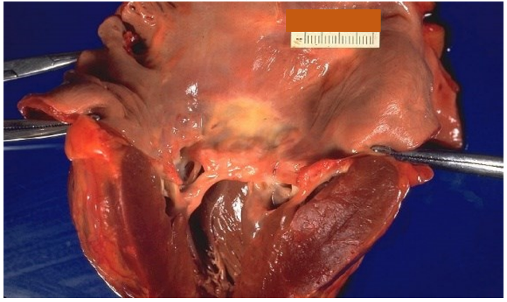
Aschoff nodule



McCallum Patch, mitral fibrosis, thickened chordae tendinae, left ventricular hypertrophy.



RHEUMATIC HEART DISEASE

MORPHOLOGY

- Gross (chronic rheumatic disease): marked valve fibrosis with commissural fusion and thickened chordae **("fish-mouth")**
- **Aschoff nodules** – round histiocyte-rich lesions within the myocardium
- **McCallum patch** – thickened, wrinkled patch in the endocardium
- **Pancarditis** during acute rheumatic fever:
  - Endocardium with small excrescences along valve line closure
  - Myocardium with Aschoff nodules
  - Pericardium with fibrinous pericarditis

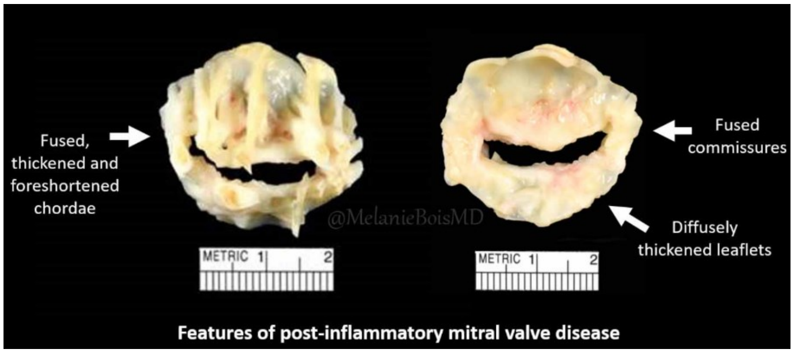
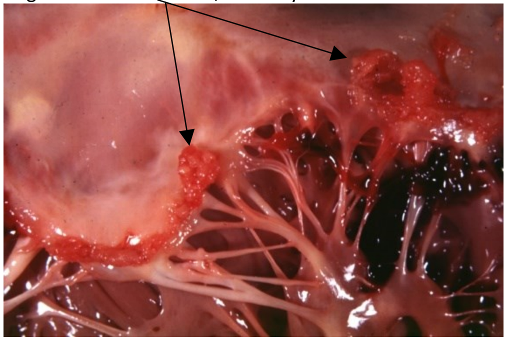

Fused, thickened and foreshortened chordae
Fused commissures
Diffusely thickened leaflets
METRIC 1 2
METRIC 1 2
@MelanieBoisMD
Features of post-inflammatory mitral valve disease

Image: Fish-mouth: post-inflammatory mitral valve disease.
Credit: Melanie Bois MD @MelanieBoisMD

Vegetations can be seen, courtesy: wikimedia foundation



OTHER HIGH YIELD POINTS

- Acute rheumatic fever due to **Group A streptococcal** infection
- 20-30 years later: scarring of the mitral and aortic valve occurs secondary to an autoimmune reaction, resulting in:
  - Mitral stenosis ± insufficiency
  - Pulmonary hypertension
  - Right ventricular hypertrophy

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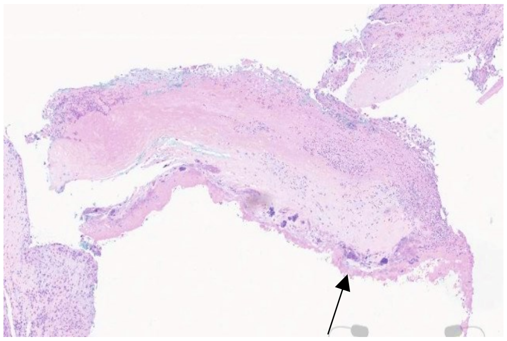
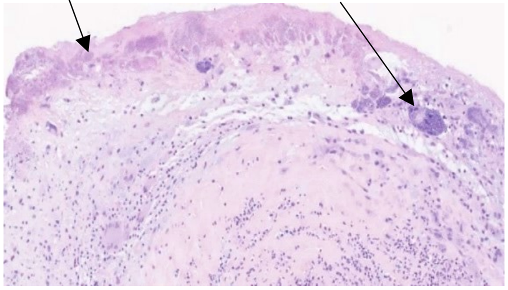
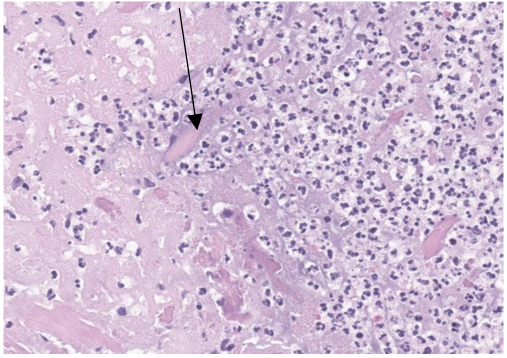
Valve appears blue and hypercellular at low power





Neutrophils with valvular destruction.



Vegetations on the endocardial surface

Link

ENDOCARDITIS

INFECTIVE ENDOCARDITIS

MORPHOLOGY

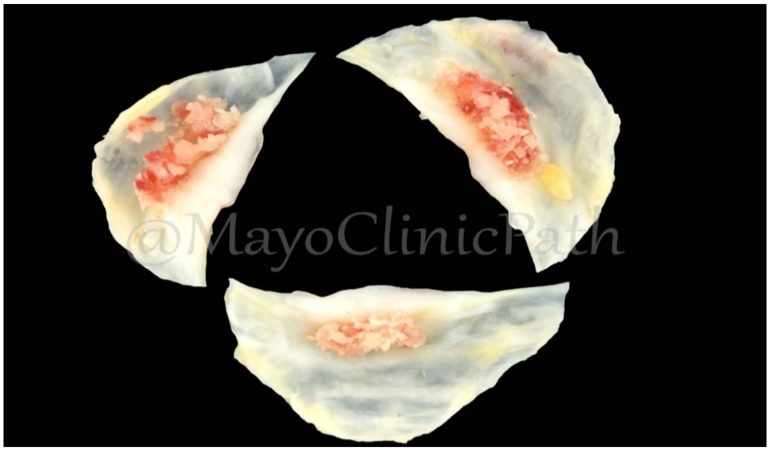
- **Neutrophils, fibrin, microorganisms on valvular tissue** with variable valve destruction (endocardial surface)]

OTHER HIGH YIELD POINTS

- Bacterial or fungal infection of the endocardium
- Most cases primarily **involve valves**
- Most common culprits: **Staphylococcus and Streptococcus**
- Common associations:
  - *Staphylococcus aureus* – intravenous drug abuse (IVDA)
  - *Staphylococcus epidermidis* – prosthetic valves
  - Viridans streptococci – subacute endocarditis
  - Enterococci – normal or previously damaged valves
  - *Streptococcus Bovis* – colon cancer
  - *Streptococcus pneumoniae* – chronic alcoholic use
  - Gram-negative endocarditis – IVDA, chronic alcohol use, immunocompromise
  - Fungal – IVDA (right-sided endocarditis), immunocompromise

DIFFERENTIAL DIAGNOSIS

- **Libman-Sacks endocarditis in lupus erythematosus**: vegetations (fibrinoid necrosis + inflammation) on **both sides of the valve** (See below image)



Credit: Division of Anatomic Pathology, Mayo Clinic

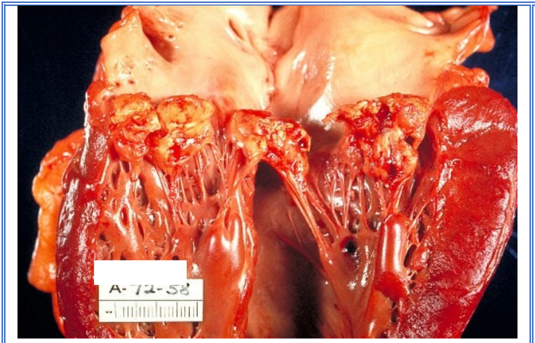


Image credits: Edwin P. Ewing, Jr

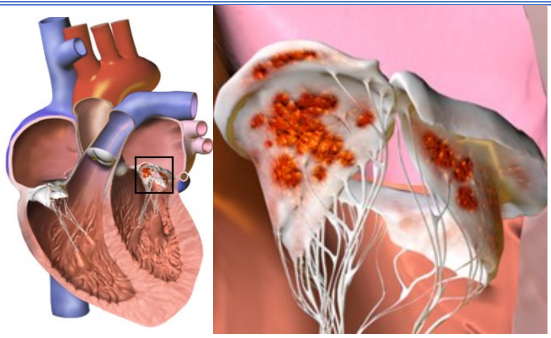
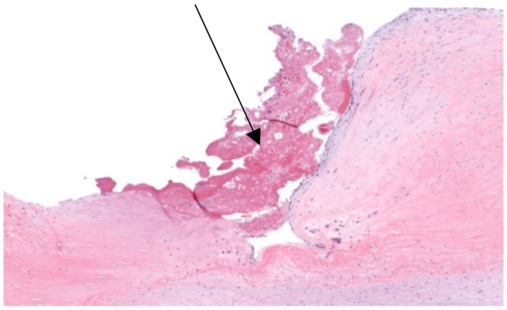


Image credits: Bruce Blaus, MD

Deposition of fibrin & platelets on the valve surface



NON-BACTERIAL THROMBOTIC (MARANTIC) ENDOCARDITIS

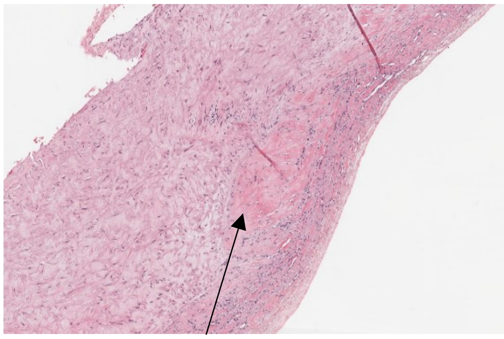
MORPHOLOGY

- **Deposition of fibrin + platelets**
- Thrombus on the surface
- No inflammation or organisms

OTHER HIGH YIELD POINTS

- Presence of **sterile thrombi on heart valves due to abnormal flow or/and hypercoagulable state**

Path Presenter



Fibrous endocardial plaques

CARCINOID HEART DISEASE

MORPHOLOGY

- **Fibrous endocardial plaques** on the leaflets of tricuspid and pulmonary valves

OTHER HIGH YIELD POINTS

- Due to secretion of **serotonin** (and related products) from a well-differentiated neuroendocrine tumor
- Usually from a small bowel tumor with liver metastases
- Can cause **right-sided heart failure**

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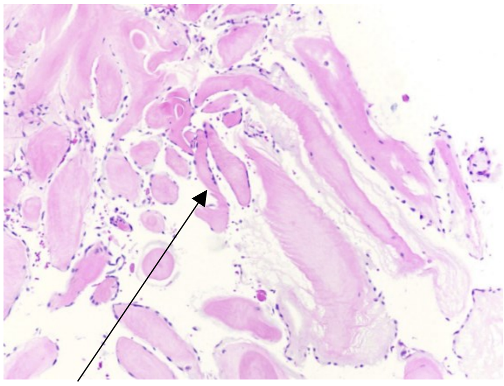
CARDIAC TUMORS



Branching fronds of avascular collagen and elastin covered with endothelium

PAPILLARY FIBROELASTOMA

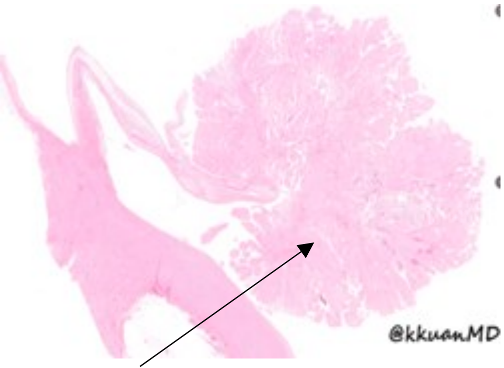
MORPHOLOGY

- Gross: resembles a **sea anemone** when submerged
- Branching fronds covered with endothelium; fronds comprise of an avascular core of collagen and elastin

OTHER HIGH YIELD POINTS

- **Most common cardiac tumor**, benign endocardial tumor; may be incidental
- Usually arises on valves on the left side of the heart
- Molecular: subset with *KRAS* mutations
- If symptomatic, due to obstruction or embolization

Path Presenter



Branching fronds

Courtesy: Kevin Kuan, MD

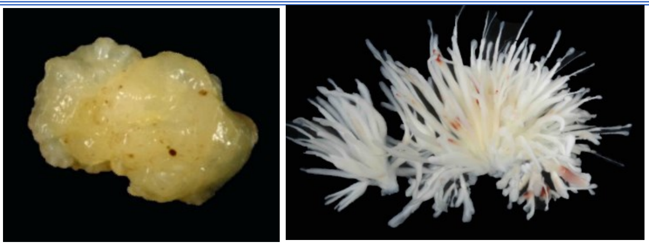


Image credits: Melanie C Bois, MD, fibroelastoma in non-aqueous and aqueous medium

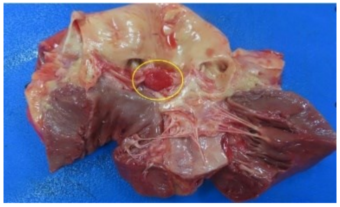


Image credits: Kevin Kuan, MD

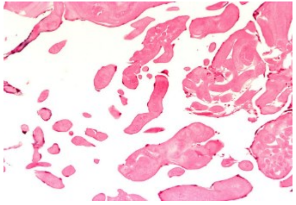
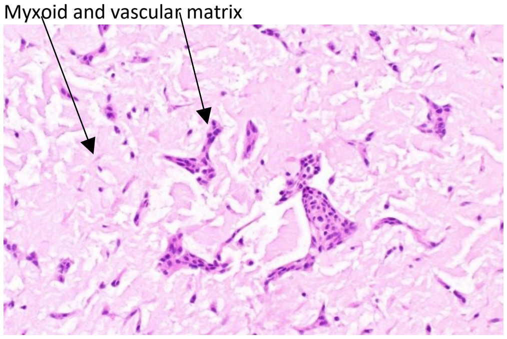
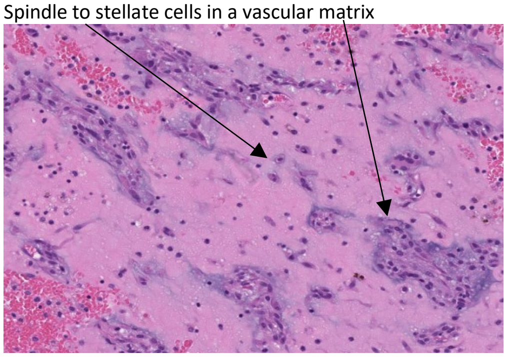


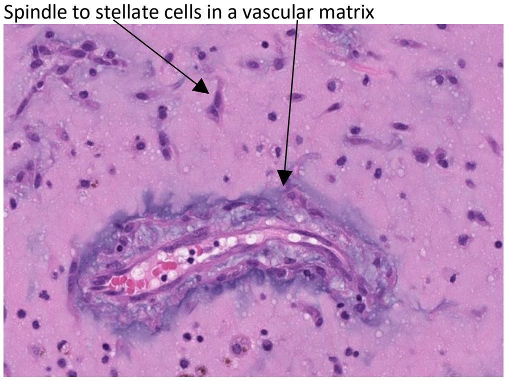
Image credits: Michael Bonert, MD



Myxoid and vascular matrix



Spindle to stellate cells in a vascular matrix



Spindle to stellate cells in a vascular matrix

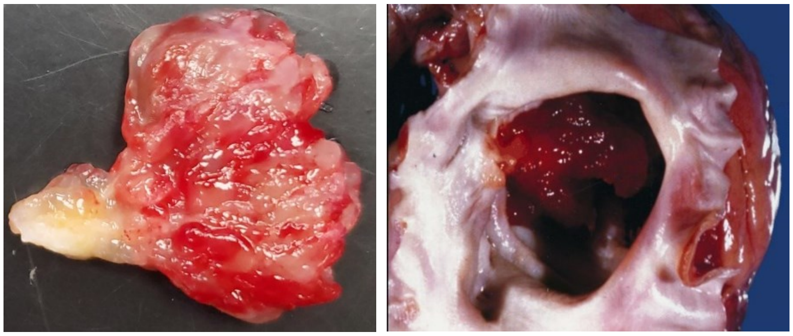
CARDIAC MYXOMA

MORPHOLOGY

- Gross: **pedunculated, sessile or villiform mass**
- **Bland stellate to plump spindled cells** ("myxoma cells") within a vascular myxoid matrix
- May see inflammatory cells, giant cells, hemorrhage, hemosiderin, calcifications, bone, and/or glandular-appearing elements
- **Matrix stains with PAS and Alcian blue**
- IHC: Myxoma cells stain with **calretinin**

OTHER HIGH YIELD POINTS

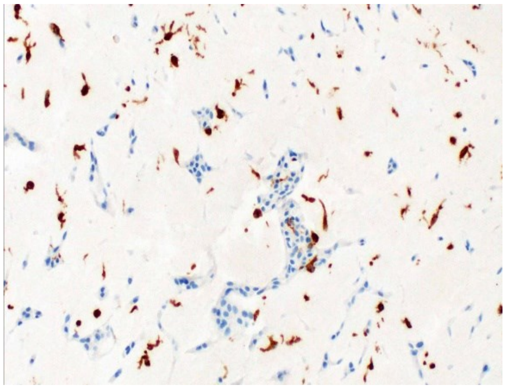
- A benign intracavitary endocardial lesion, usually in the **left atrium**
- **Second most common heart tumor**
- Mostly sporadic; some can arise in the setting of **Carney's Syndrome, familial myxomatous syndrome, or tuberous sclerosis complex**
- If symptomatic, due to obstruction of blood flow or embolization
- A subset of patients with cardiac myxomas has **Carney complex (CNC)**. This is diagnosed via a **germline mutation in PRKAR1A**. A patient with CNC is at risk for multiple cardiac myxomas; so are their first-degree relatives if they also carry the mutation. We can detect this mutation with IHC. Loss of staining in tumor cells is associated with a germline mutation
- Recurrence after resection is relatively rare



Credit: Kevin Kuan, MD

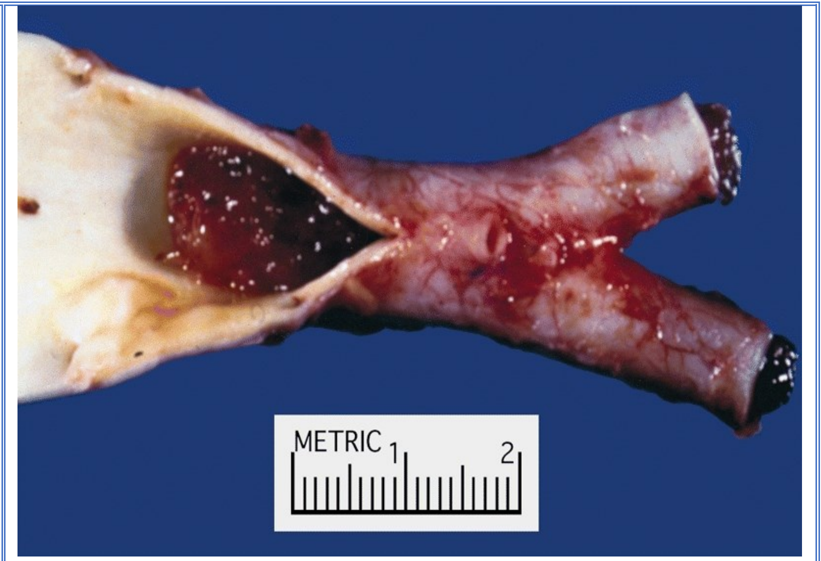
Link

PRKAR1A immunohistochemical stain

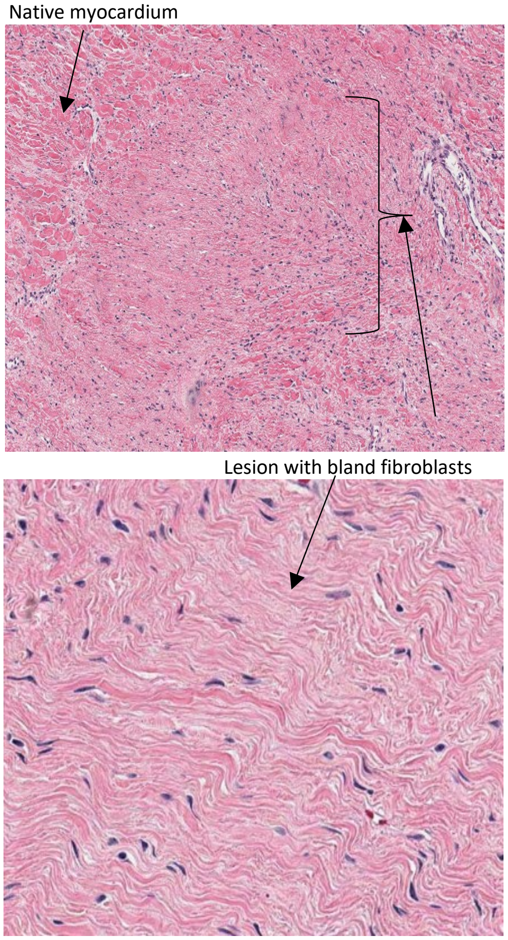


Credit: Melanie Bois MD @MelanieBoisMD

Path Presenter



Embolization of myxoma



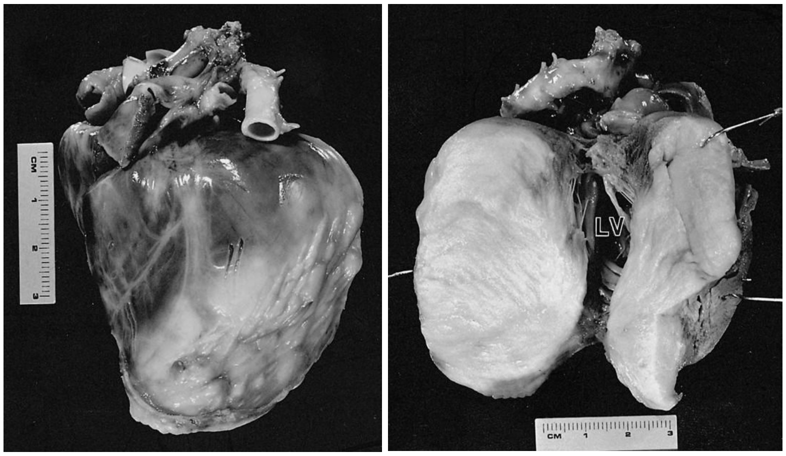
CARDIAC FIBROMA

MORPHOLOGY

- Gross: **Circumscribed ventricular septal mass**
- **Bland fibroblasts** in a variably collagenized stroma may infiltrate the myocardium; microcalcifications common
- IHC: (+) SMA

OTHER HIGH YIELD POINTS

- Benign, usually occurs in the **ventricular septum of children**
- Often large and can interrupt conduction/contraction
- Associated with **Gorlin syndrome** (nevoid basal cell carcinoma syndrome) due to germline ***PTCH1* gene** mutations



Courtesy: AFIP public images, Large septal mass on the anterior and right lateral border

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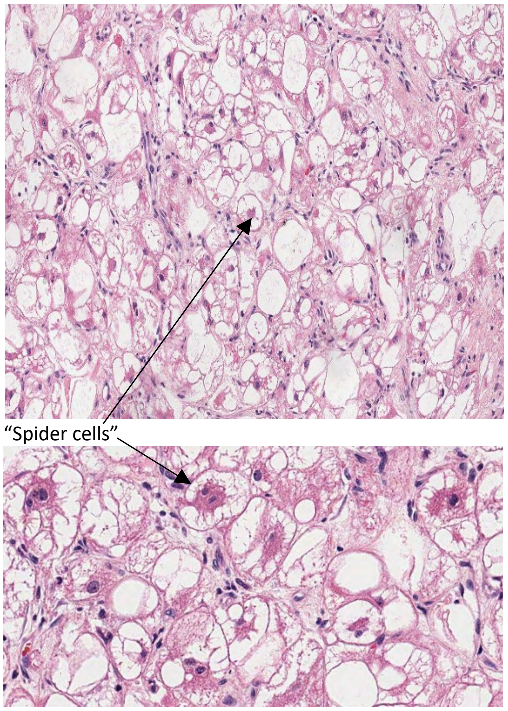

"Spider cells"

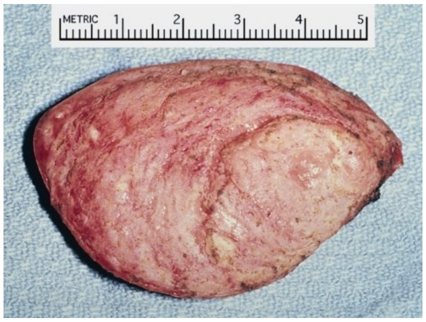
CARDIAC RHABDOMYOMA

MORPHOLOGY

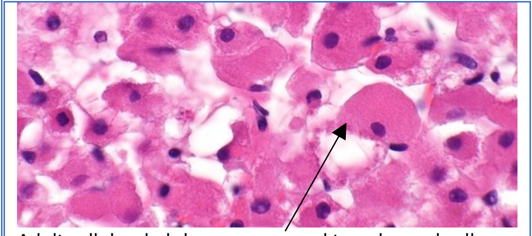
- Large, vacuolated "**spider**" cells with radial sarcoplasmic extensions from the nucleus to the cytoplasmic membrane
- **IHC:** (+) desmin and SMA; PAS highlights cytoplasmic glycogen

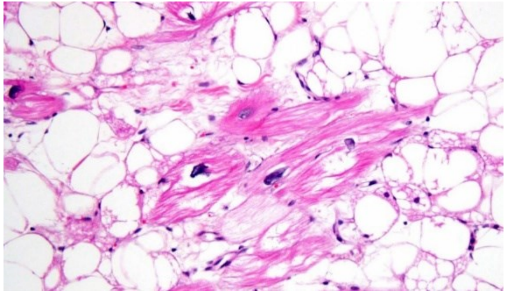
OTHER HIGH YIELD POINTS

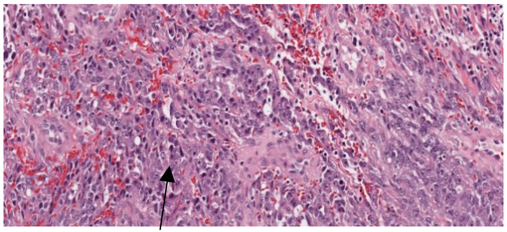
- **Most common cardiac tumor in children**, usually in ventricular myocardium; benign
- Thought to be a hamartoma of developing myocytes
- Often arising in the setting of **tuberous sclerosis (germline *TSC1* or *TSC2* mutations)**


Round or lobulated, well-circumscribed mass
Courtesy: Nima Nasiri, M.D

Path Presenter


Adult cellular rhabdomyoma: round to polygonal cells

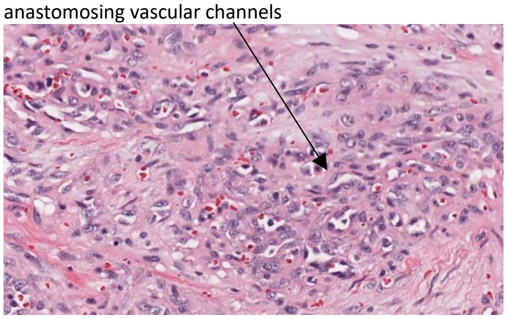

Lipomatous hypertrophy of atrial septum
Credit: Melanie Bois MD @MelanieBoisMD


Angiosarcoma: Malignant epithelioid cells

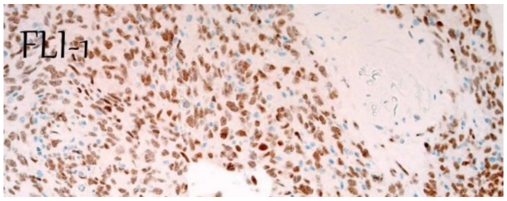
OTHER CARDIAC TUMORS & MASS LESIONS

- **Metastases** – most common malignancy of the heart (lung, melanoma, sarcoma, renal cell carcinoma)
- **Lipoma** – benign, encapsulated proliferation of mature adipose tissue; if in atrial septum with brown fat + mature fat + atrial myocytes = lipomatous hypertrophy of the atrial septum
- **Adult cellular rhabdomyoma** – benign neoplasm of striated muscle; cellular proliferation of round to polygonal cells with prominent vascularity; adults; no history of tuberous sclerosis
- **Hemangioma** – benign proliferation of thin-walled vascular spaces
- **Angiosarcoma** – malignant cells with vascular differentiation; most common cardiac sarcoma most commonly arise in the right atrium, generally near the atrioventricular groove
- **Leiomyosarcoma**
- **Undifferentiated pleomorphic sarcoma**
- **Diffuse large B cell Lymphoma**
- **Lipomatous hamartoma of the atrioventricular valve** – unencapsulated fat in AV valve
- **Hamartoma of mature cardiac myocytes** – a discrete nodular collection of disorganized myocytes forming a mass
- **Cardiac hamartoma – a** discrete collection of mature mesenchymal tissues in the heart
- **Conduction system hamartoma** – collections of pale, eosinophilic Purkinje cells distributed along the endocardium; usually, children
- **Cystic tumor of the atrioventricular node** – endodermal inclusion forming a cystic lesion within the AV septum

anastomosing vascular channels



FLI-1 immunostain



Credit: Melanie Bois MD @MelanieBoisMD

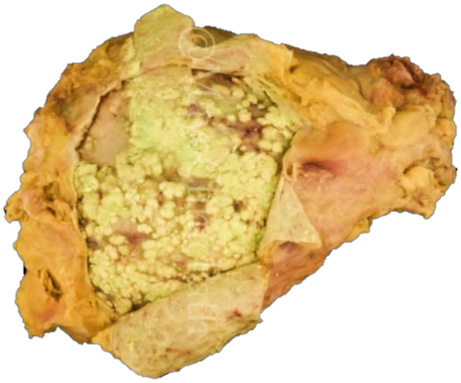


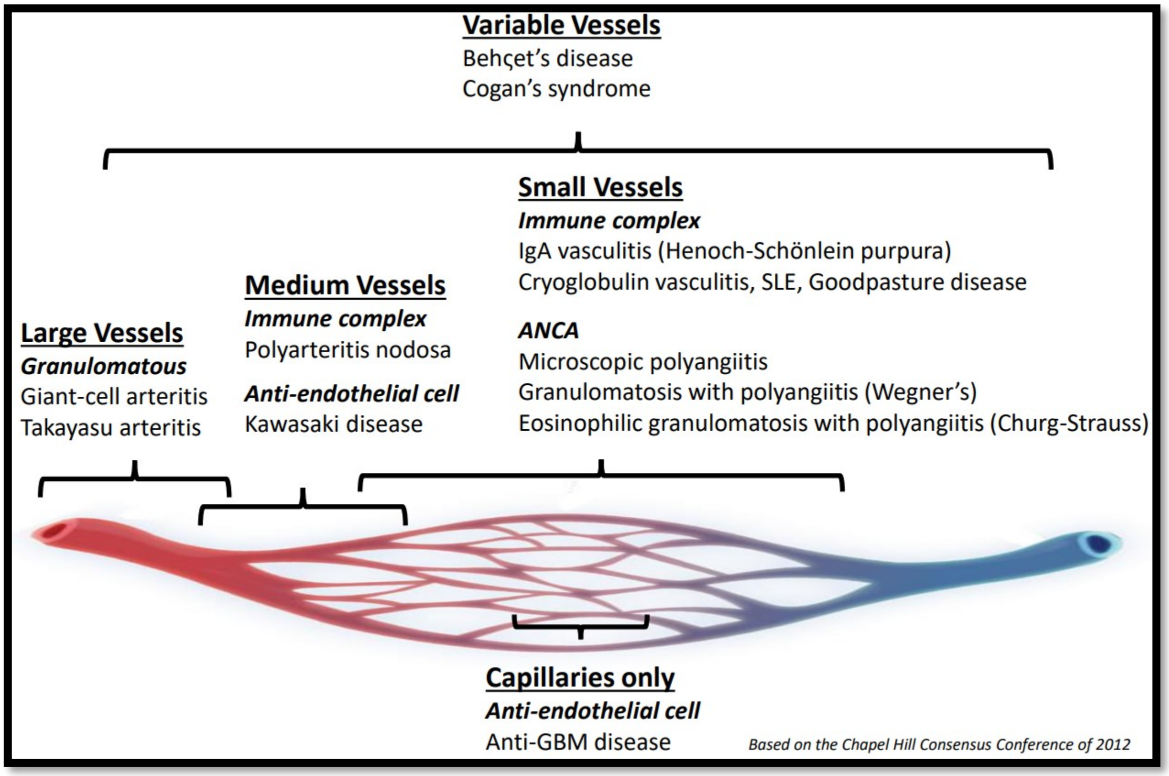
Image: Nodular deposits of a pulmonary squamous cell carcinoma involving the pericardium & epicardium. Credit: Division of Anatomic Pathology, Mayo Clinic

Path Presenter

VASCULITIS

HIGH YIELD POINTS

- Vasculitis is defined as inflammation of the blood vessel walls
- It can be infectious or non-infectious
- Diverse clinical findings: constitutional symptoms, localized tissue damage due to ischemia or bleeding leading, single or multiorgan dysfunction, elevated CRP and ESR
- Many systemic rheumatologic diseases (e.g., rheumatoid arthritis, lupus, sarcoidosis) can have associated vasculitis



Variable Vessels
Behçet's disease
Cogan's syndrome

Large Vessels
Granulomatous
Giant-cell arteritis
Takayasu arteritis

Medium Vessels
Immune complex
Polyarteritis nodosa
Anti-endothelial cell
Kawasaki disease

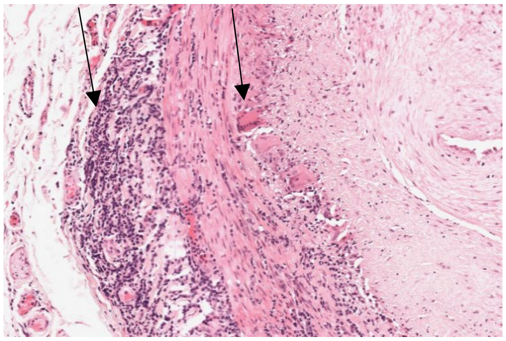
Small Vessels
Immune complex
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulin vasculitis, SLE, Goodpasture disease
ANCA
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegner's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Capillaries only
Anti-endothelial cell
Anti-GBM disease

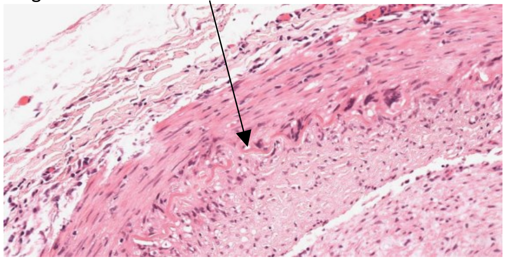
Based on the Chapel Hill Consensus Conference of 2012

10. CARDIOVASCULAR PATHOLOGY

GCA: Lymphocytic and granulomatous inflammation



Fragmentation of internal elastic lamina



Credits: Adelita Vizcaino MD @astroade

LARGE CELL VASCULITIS

MORPHOLOGY

- **Lymphohistiocytic inflammation of the vessel wall** with frequent granulomas/giant cells, nodular thickening of the intima and medial scarring, fragmentation of internal elastic lamina (best seen on Elastic stain); changes may be patchy

GIANT CELL ARTERITIS

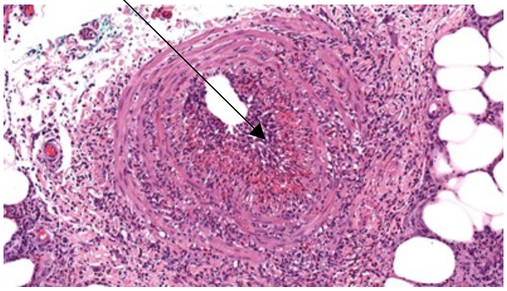
- Usually affects **aorta and/or its major branches**, with a predilection for the branches of the carotid and vertebral arteries, especially the **temporal artery**
- Onset is usually after the **age of 50 years**
- Most common vasculitis in the elderly in the United States
- Often associated with polymyalgia rheumatica
- Involvement of the ophthalmic artery can cause permanent blindness (**medical emergency** requiring prompt diagnosis and treatment)

TAKASAYU ARTERITIS

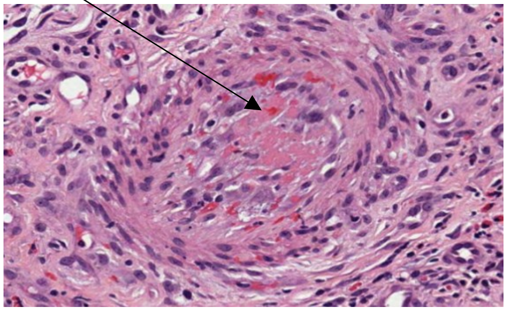
- Predominantly affects **aortic arch and major branches**
- Onset is usually **before the age of 50 years**
- Transmural fibrous thickening of the aorta with lumen narrowing, particularly of branching vessels and loss of pulses in upper extremities

Path Presenter

Transmural mixed inflammation



Fibrin Thrombus



MEDIUM VESSEL VASCULITIS

MORPHOLOGY

- **Transmural necrotizing arteritis** of **medium or small** arteries (**without glomerulonephritis** or vasculitis of arterioles, capillaries, or venules) with mixed inflammation, fibrinoid necrosis, and thrombosis
- Involves main **visceral arteries** and their branches
- **Inflammatory aneurysms and stenoses** are common

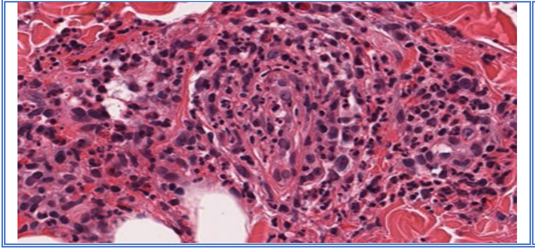
POLYARTERITIS NODOSA

- Frequently involves **renal artery and GI vasculature**
- Often **patchy/segmental**
- Immune-complex mediated
- ~30% have chronic hepatitis B

KAWASAKI DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME)

- Usually **< 4 years old**, often post-infectious
- Present with oral, conjunctival, and palmoplantar erythema **("strawberry tongue")** with a desquamative **rash** and **cervical lymphadenopathy**
- Predominantly coronary arteries involved → aneurysms & MI
- Autoantibodies to endothelial/smooth muscle cells
- Treat with IVIG and aspirin

Path Presenter



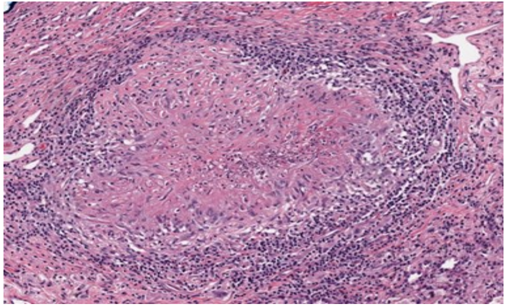
SMALL VESSEL VASCULITIS

ANCA-MEDIATED

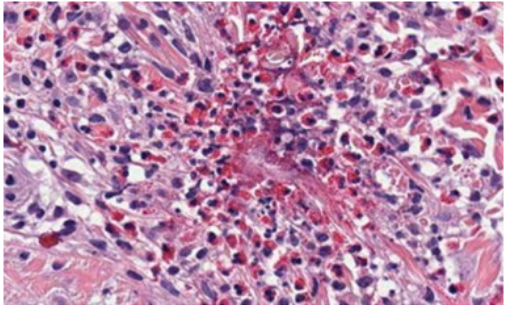
MICROSCOPIC POLYANGIITIS (MPA)

- **Neutrophil predominant** and **leukocytoclastic** with **fibrinoid necrosis**, **thrombosis**, and **red blood cell extravasation**
- Very commonly involves the **kidneys and lungs**
- **MPO-ANCA** usually positive

Necrotizing granulomatous inflammation and vasculitis (GPA)



Eosinophil-rich and necrotizing granulomatous inflammation (EGPA)



Path Presenter

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

- **Necrotizing granulomatous inflammation + vasculitis**
- Commonly impacts **lung, nasal cavity,** and **kidney**
- In the lung/head, granulomas with geographic central necrosis and associated vasculitis → form ulcers and nodules
- In the kidney, one can see **crescentic glomerulonephritis**
- **PR3-ANCA** positive

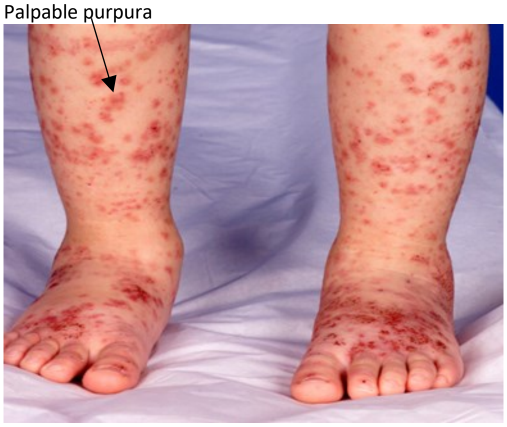
Path Presenter

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS)

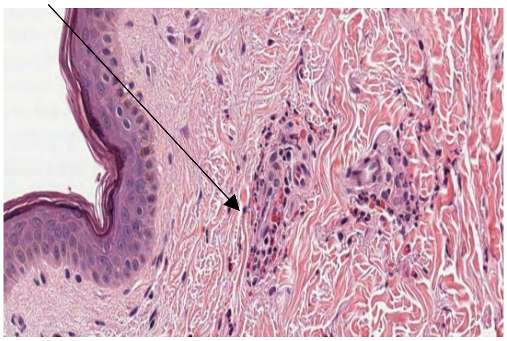
- **Eosinophil-rich and necrotizing granulomatous inflammation**
- Often affects the **lung**
- Associated with asthma and eosinophilia
- **MPO-ANCA** usually positive

Path Presenter

Palpable purpura



Vasculitis



IMMUNE COMPLEX-MEDIATED VASCULITIS

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA)

- **Vasculitis** with **IgA1-dominant immune-deposits**
- Often involves skin (palpable purpura), GI tract (abdominal pain), kidneys, and joints (arthritis)
- **Most common systemic vasculitis in children**
- Usually post-infectious (often after upper respiratory infection) and self-limited

Path Presenter

CRYOGLOBULINEMIC VASCULITIS

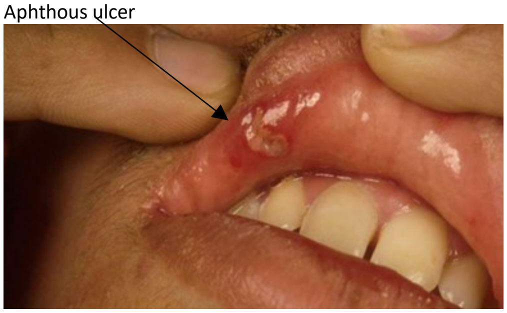
- **Serum cryoglobulins (Ig that precipitate out of solution at < 37°C)** → vessel deposits → vasculitis
- Often **involves skin, kidney, and peripheral nerves**
- Highly associated with **Hepatitis C and monoclonal gammopathy**

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS

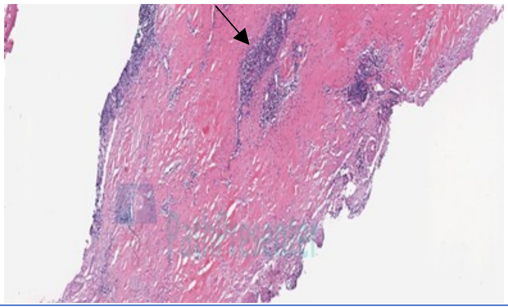
- Associated with **anti-C1q antibodies**
- Immune complex→ activate complement cascade→ mast cell degranulation and neutrophilic activation→ urticaria and small vessel vasculitis

Path Presenter

Aphthous ulcer



IgG4-related aortitis with dense lymphoplasmacytic infiltrate in the vessel wall



VARIABLE VESSEL VASCULITIS

BEHCET'S DISEASE

- **Vasculitis** involving **arteries or veins** of **any size**
- Recurrent oral and/or genital **aphthous ulcers**, accompanied by cutaneous, ocular, articular, GI, and/or CNS lesions
- Can get thrombosis or aneurysms
- Most common along the "**ancient silk road**" (Middle east → Asia)

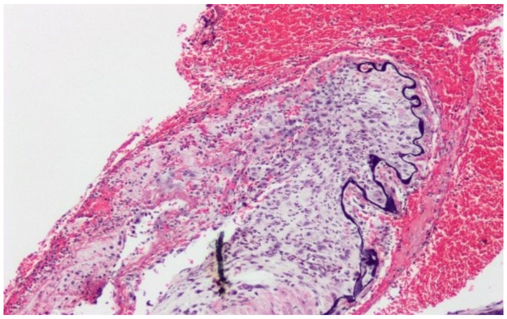
Path Presenter

COGAN'S SYNDROME

- Systematic vasculitis with predominantly **ocular and inner ear** findings
- May involve the aorta and heart

IgG4-RELATED AORTITIS/PERIAORTITIS

- Most often seen in **older men**
- Characteristic findings in the adventitia: dense lymphoplasmacytic infiltrate, **storiform-type** fibrosis, and **obliterative phlebitis**
- Must see **> 50 IgG4+ plasma cells** in a single high-power field

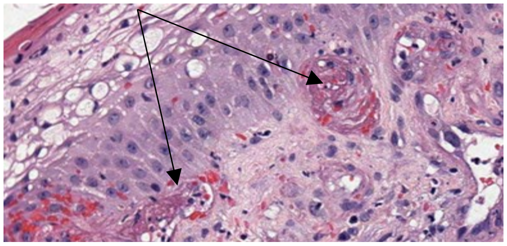


INFECTIOUS VASCULITIS

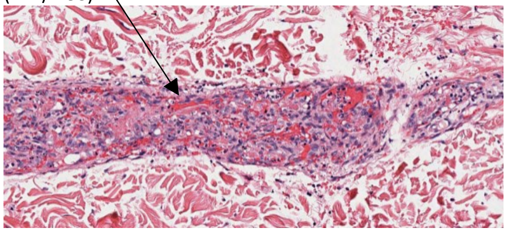
- Most often, due to direct extension of infected tissue; can cause aneurysms **("mycotic" aneurysms** - figure)
- Infections where vasculitis is an important part of the disease:
  - **Syphilis –** luminal obstruction and perivascular infiltrate of lymphocytes and plasma cells
  - **Fungi –** aspergillus and mucor can cause disseminated infection with angioinvasion and tissue necrosis, usually immunocompromised patients
  - **Other examples –** Rocky Mountain spotted fever, Q fever, Typhus, Meningococcus, Lyme disease

COAGULOPATHIC DISORDERS

Bland thrombi in vessels (DIC/TTP)



Thrombotic microangiopathy of the blood vessel (TTP/HUS)



MORPHOLOGY

- All coagulopathic disorders show bland (non-inflamed) thrombi in vessels

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- Consumptive coagulopathy, where **systemic activation of the coagulation cascade** leads to **thrombosis of small vessels throughout the body**
- It can occur in many settings (e.g., sepsis, trauma, etc.)

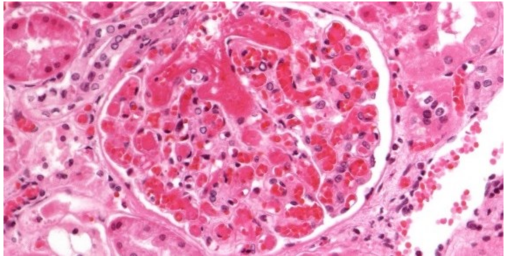
Path Presenter

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- **Thrombotic microangiopathy** (TMA) with widespread **fibrin thrombi** in small vessels, intimal proliferation, mucoid changes, and entrapped **fragmented red blood cell fragments**, or frank necrosis
- Fever, hemolytic anemia, purpura, thrombocytopenia, renal dysfunction
- **ADAMTS13 deficiency**

Path Presenter

Microthrombi in glomerular capillaries (DIC/TTP/HUS)



HEMOLYTIC UREMIC SYNDROME (HUS)

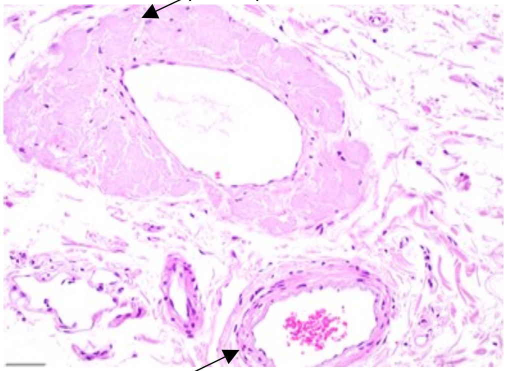
- Similar to TTP, but **thrombi are mostly limited to kidneys**
- Usually, in kids, after eating **E. Coli O157:H7** (A Shiga-like toxin that damages endothelial cells), which also causes **bloody diarrhea**

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

- **Antibodies recognize heparin + platelet factor 4 complexes** → activate platelets → thrombocytopenia and thrombus formation
- Usually, **thrombi are in large vessels** (e.g., DVT → PE)

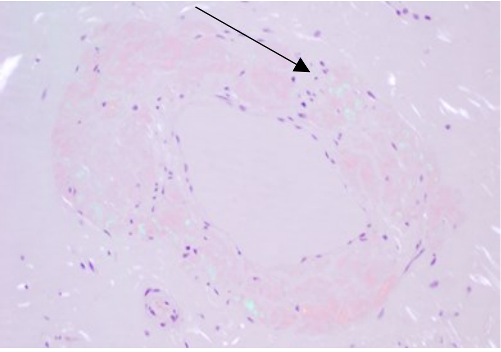
VASCULAR DEPOSITION DISORDERS

Blood vessel with amyloid deposition

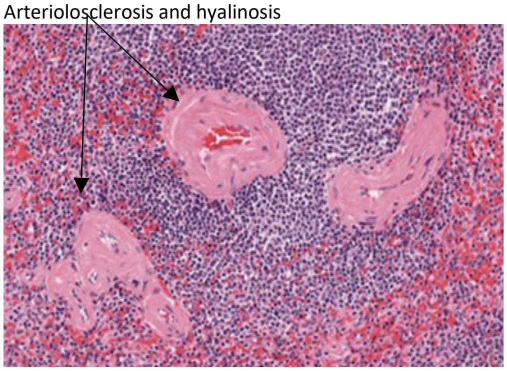


Uninvolved vessel

Apple-green birefringence under polarization



Arteriolosclerosis and hyalinosis



AMYLOIDOSIS

MORPHOLOGY

- **Extracellular eosinophilic amorphous material**
- Congo red: **"apple-green" birefringence**; gray on trichrome

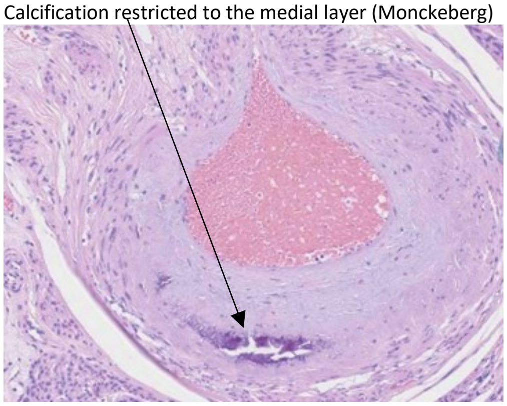
OTHER HIGH YIELD POINTS

- Deposition of **abnormally folded protein** (**rich in ß-sheets**) in vessels and tissues → obstructs the flow and creates rigidity (impaired vasoreactivity) → ischemic injury
- It also makes vessels brittle → hemorrhage
- Subtype (see below) to determine etiology using **immunofluorescence, mass spectrometry, immunoblotting, IHC,** etc
- Differential diagnosis: hypertensive changes (intimal fibroplasia of small arteries and hyalinization of arterioles)

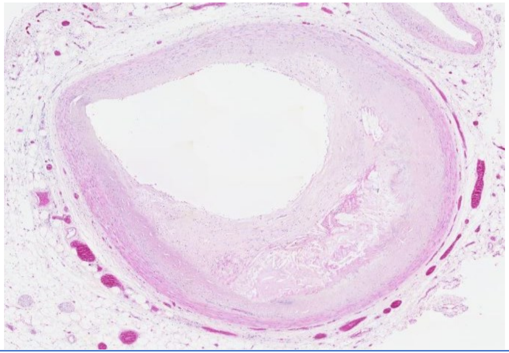
Systemic Amyloidosis			
Plasma cell dyscrasia	AL	Ig light chains (λ > κ)	Multiple myeloma
Reactive systemic amyloidosis	AA	Serum amyloid A (SAA)	Chr inflammatory conditions
Hemodialysis associated	Aβ2m	β2-microglobulin	Chronic renal failure
Localized Amyloidosis			
Senile cerebral	Aβ	Amyloid (APP) precursor protein	Alzheimer's disease
Endocrine	A/IAPP ACal	Islet amyloid Calcitonin	Type 2 diabetes Medullary thyroid ca
Isolated atrial	AANF	ANP	Can cause arrhythmias
Hereditary Amyloidosis			
Familial Mediterranean fever	AA	Serum amyloid A (SAA)	Auto Rec MEFV gene
Familial amyloidotic neuropathy	ATTR	Transthyretin	Auto Dom, ATTR gene most common

Path Presenter

Calcification restricted to the medial layer (Monckeberg)



Atherosclerosis: (where calcification is in the intima and then subsequently involves the media



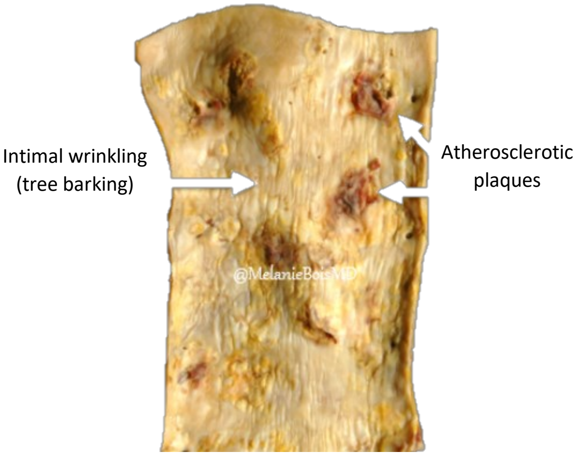
MÖNCKEBERG ARTERIOSCLEROSIS

MORPHOLOGY

- **Calcification of the medial arterial layer**

OTHER HIGH YIELD POINTS

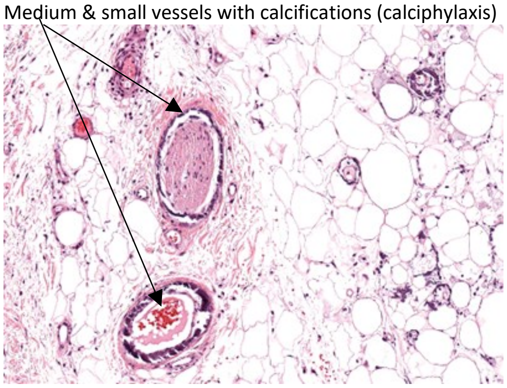
- Common and often incidental in older patients
- Associated with **age, diabetes, renal failure, and hyperparathyroidism**
- Differential diagnosis: atherosclerosis (where calcification is in the intima and then subsequently involves the media, see below image)



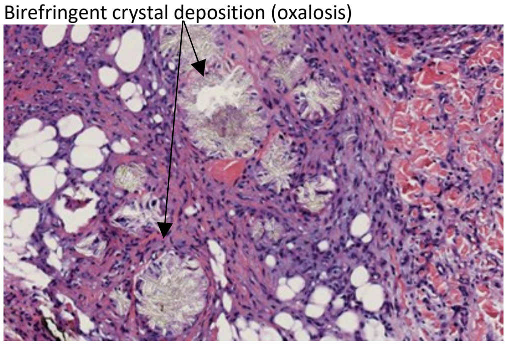
Credit: Melanie Bois MD @MelanieBoisMD

Path Presenter

Medium & small vessels with calcifications (calciphylaxis)



Birefringent crystal deposition (oxalosis)



OTHER UNCOMMON DEPOSITION DISORDERS

LIGHT CHAIN-DEPOSITION DISEASE

- It looks similar to amyloid on H&E but is **Congo red negative**
- Due to immunoglobulin light chain deposits in tissue in non-amyloid form → seen in association with **Ig-producing neoplasms, usually κ light chain**

CALCIPHYLAXIS

- Calcification of small to medium-sized vessels
- Usually, a result of **hyperparathyroidism in chronic renal failure**
- Also, see thrombi, soft tissue calcifications, panniculitis, necrosis, and ulceration

Path Presenter

OXALOSIS

- **Birefringent crystal deposition** in tissue and vessels with foreign body giant cell reaction
- It can lead to occluded lumen and ischemia
- Etiology:
    - ➢ **Primary** – due to enzyme deficiency
    - ➢ **Secondary** – due to ingestion of oxalates or ethylene glycol (antifreeze)

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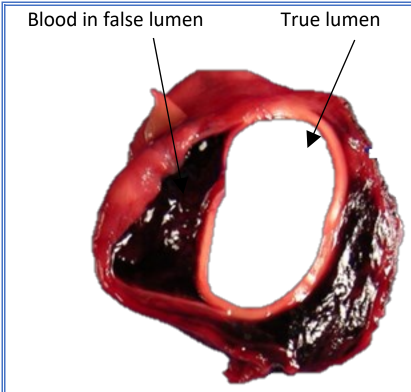
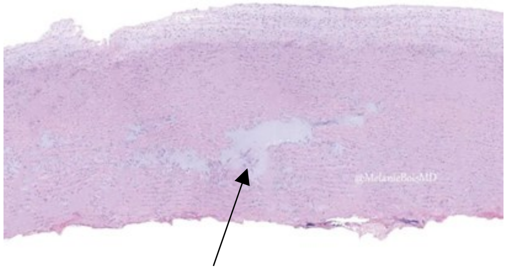

Blood in false lumen
True lumen

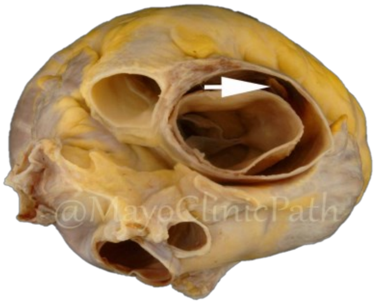
Credit: Cory Nash, MS, PA (ASCP)


@MelanieBoisMD
Cystic medial degeneration

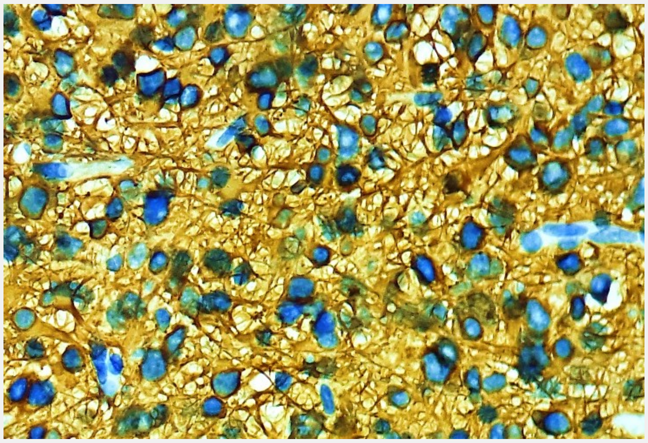
Credit: Melanie Bois MD @MelanieBoisMD

ARTERIAL DISSECTION

- Often caused by cystic medial degeneration:
  - **Marked loss of elastic lamellae (elastic stain)**
  - Deposition of proteoglycans (colloidal iron stain)
- **Disruption of vessel lumen** → blood can enter "false lumen" and **dissect between layers or rupture**
- Frequently caused by **trauma** but can be sporadic
- Common sites:
  - Cervical (carotid/vertebral arteries): **often, young adults**
  - Coronary arteries
  - Aorta: **males with hypertension, Marfan syndrome, and bicuspid aortic valve**
- **Stanford Type A**: involves ascending aorta (more common)
- **Stanford Type B**: involves the descending aorta


@MayoClinicPath

Credit: Division of Anatomic Pathology, Mayo Clinic



GFAP immunostain in Anaplastic Astrocytoma. Image courtesy: Akanksha Gupta, MD

CHAPTER 11: NEUROPATHOLOGY

Jared T. Ahrendsen, MD, PhD
Akanksha Gupta, MD

11. NEUROPATHOLOGY

DIFFERENTIAL DIAGNOSIS BY CLINICAL INFORMATION

Location	Pediatric/Young Adult	Older Adult
Cerebral/ Supratentorial	Ganglioglioma, DNET, PXA, ependymoma, AT/RT CNS Embryonal Neoplasms	GBM, infiltrating astrocytoma (grades 2-4), oligodendroglioma, metastases, lymphoma, infection
Cerebellar/ Infratentorial/ Fourth ventricle	PA, medulloblastoma, ependymoma, choroid plexus papilloma, AT/RT	Metastases, hemangioblastoma, choroid plexus papilloma, subependymoma
Brainstem	PA, DMG	Astrocytoma, GBM, DMG, metastases
Spinal cord (intramedullary)	Ependymoma, PA, DMG, MPE, drop metastases	Ependymoma, astrocytoma, DMG, MPE, paraganglioma
Spinal cord (extramedullary)	Meningioma, schwannoma, metastases, melanocytoma/melanoma	Schwannoma, meningioma, melanocytoma/melanoma, MPNST
Spinal cord (extradural)	Bone tumor, meningioma, abscess, vascular malformation	Herniated disk, lymphoma, abscess, metastases
Extra-axial/Dural/ Leptomeningeal	Leukemia/lymphoma, Ewing sarcoma, rhabdomyosarcoma, disseminated medulloblastoma, DLGNT	Meningioma, SFT, metastases, lymphoma
Sellar/infundibular	Pituitary adenoma, craniopharyngioma, Rathke cleft cyst, pituicytoma, LCH, germ cell tumors	Pituitary adenoma, craniopharyngioma, Rathke cleft cyst, pituicytoma, meningioma, metastases, chordoma
Suprasellar/ Hypothalamic/ Optic pathway/ Third ventricle	Germ cell tumors, craniopharyngioma, PA/optic pathway glioma, LCH	Colloid cyst, craniopharyngioma, chordoid glioma
Pineal	Germ cell tumors, pineocytoma, pineoblastoma, pineal cyst	Pineocytoma, pineal cyst, PPTID
Thalamus	PA, DMG	DMG, GBM, lymphoma
Lateral ventricle	Central neurocytoma, SEGA, choroid plexus papilloma/carcinoma, meningioma	Central neurocytoma, SEGA, choroid plexus papilloma, subependymoma, meningioma
Nerve root/ Paraspinal	Neurofibroma, schwannoma, MPNST	Neurofibroma, schwannoma, MPNST, lymphoma, meningioma
Cerebellopontine angle	Schwannoma, choroid plexus papilloma, AT/RT	Schwannoma, meningioma, epidermoid cyst, choroid plexus papilloma, endolymphatic sac tumor

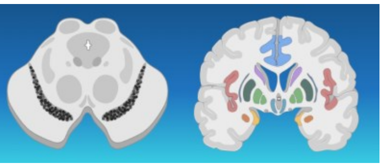
Modified from: Practical Surgical Neuropathology: A Diagnostic Approach. Second Edition. 2018.

PA: Pilocytic Astrocytoma
PXA: Pleomorphic Xanthoastroctyoma
DNET: Dysembryoplastic Neuroepithelial Tumor
GBM: Glioblastoma
AT/RT: Atypical Teratoid/Rhabdoid Tumor
DMG: Diffuse Midline Glioma (H3 K27M mutant)
SEGA: Subependymal Giant Cell Astrocytoma
MPE: Myxopapillary Ependymoma
MPNST: Malignant Peripheral Nerve Sheath Tumor
SFT: Solitary Fibrous Tumor
LCH: Langerhans Cell Histiocytosis
PPTID: Pineal Parenchymal Tumor of Intermediate Differentiation
DLGNT: Diffuse Leptomeningeal Glioneuronal Tumor

IMAGING FINDINGS:

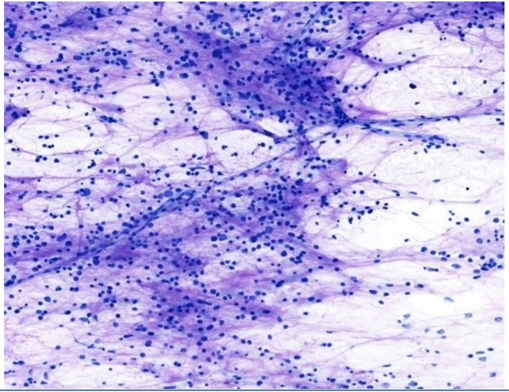
Metastasis: multiple enhancing/rim enhancing nodules at grey white junction in cerebrum
Lymphoma: periventricular enhancing lesion
Glioblastoma: rim enhancing, "butterfly" mass
Meningioma: dural lesion with a " dural tail" (enhancing)
Myxopapillary ependymoma: "sausage-shaped" filum terminale mass
Pilocytic astrocytoma: Circumscribed, cystic brain mass in the cerebellum of a child or young adult
Ganglioglioma: Child with epilepsy and a temporal lobe cystic mass with enhancing "mural" nodule

11. NEUROPATHOLOGY



IS THIS TUMOR GLIAL?

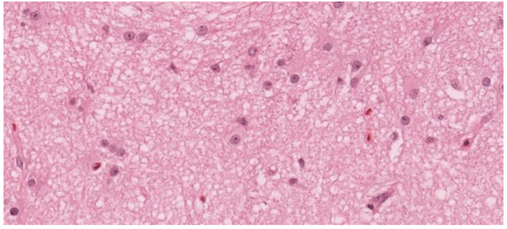
Fibrillary processes with naked nuclei



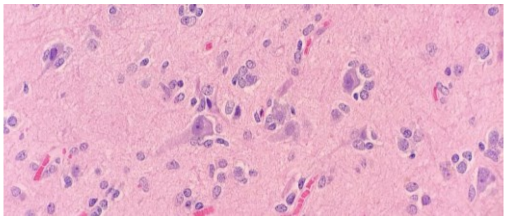
- As opposed to metastases & other non-glial tumors, glial tumors often have:
  - **Fibrillary processes**
  - Often also naked nuclei
  - Best appreciated on **cytology** (squash prep)
  - **Infiltrative** growth into brain parenchyma with entrapped tumoral axons (neurofilament +; primarily seen with GBM, infiltrating astrocytomas, and oligodendroglioma) (vs **non glial tumors and circumscribed gliomas, which are usually well demarcated**)
  - **Secondary structures**, such as: perineuronal satellitosis, subpial density, perivascular collections, infiltration along white matter tracts
  - Eosinophilic cytoplasm with nuclear hyperchromasia/pleomorphism
  - IHC: **GFAP and/or Olig2 positive** (warning: broad spectrum cytokeratins may stain glial filaments as they are both intermediate filaments)

ARE THESE GLIAL CELLS NEOPLASTIC?

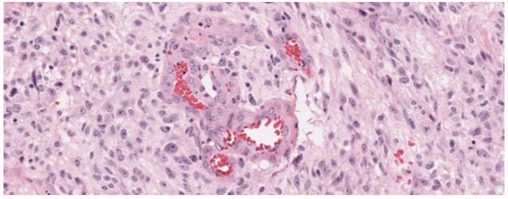
Reactive gliosis



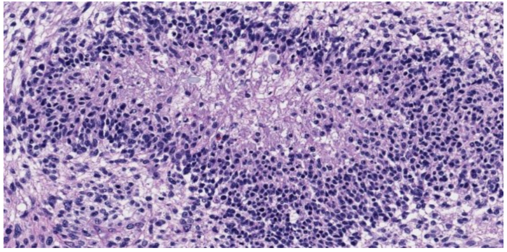
Perineuronal satellitosis



Microvascular proliferation



Pseudopalisading necrosis



Path Presenter

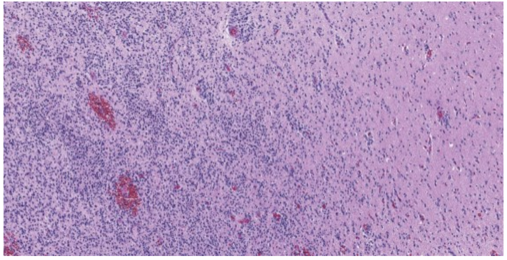
PP Link PP Link PP Link PP Link

- **Gliosis** = **reactive** changes of glial cells (astrocytes and microglia) in response to injury
  - Includes both **proliferation** and **hypertrophy** of glial cells
- This can histologically mimic a tumor and pose a diagnostic dilemma, especially intraoperatively
- This is particularly troublesome as gliosis can be found **adjacent to tumors** or as part of **reactive process** that can mimic tumors radiographically
- **Early reactive astrocytosis:** hypertrophy with enlarged cytoplasm/processes and open chromatin with prominent nucleoli
- **Longer term reactive astrocytosis:** astrocytes become gemistocytic with large amounts of brightly eosinophilic eccentric cytoplasm (Warning: some tumors can appear gemistocytic too!)
- **Chronic reactive astrocytosis:** often seen around slow-growing lesions
  - → more fibrillar with long astrocytic processes and Rosenthal fibers
  - → *"piloid gliosis"*

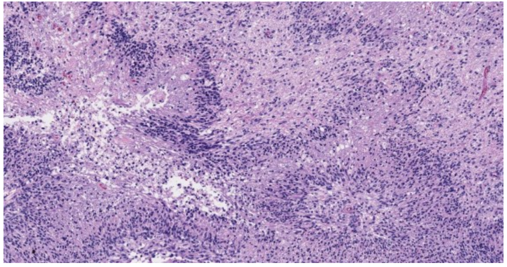
Gliosis	Glioma
Euchromatic, open chromatin, round/ovoid nuclei with generally smooth contours	Large, hyperchromatic, variable chromatin, often angulated nuclei with irregular contours
Evenly spaced astrocytes	Clustering of astrocytes, hypercellular, satellitosis
Abundant eosinophilic cytoplasm	"Naked" nuclei
Astrocytes with variable atypia	Uniform atypia
No mitotic activity	Possible mitoses
Radially oriented fibrillary processes	Necrosis and/or microvascular proliferation (usually in high grades)
Other reactive changes, such as inflammation, macrophages, demyelination, etc.	Demonstratable mutation (e.g., IDH1 R132H, ATRX, TP53, etc.)

ADULT-TYPE DIFFUSE GLIOMAS

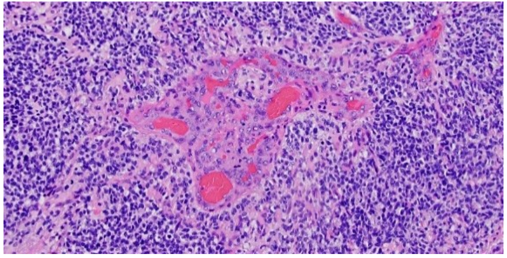
Infiltrative edge



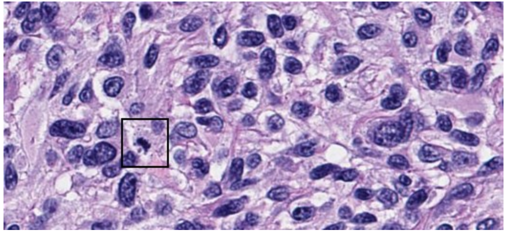
Pseudo palisading necrosis



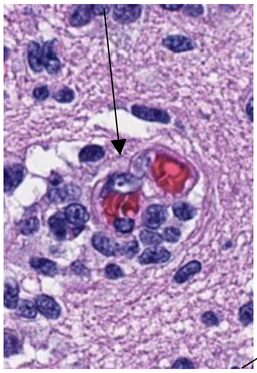
Microvascular proliferation



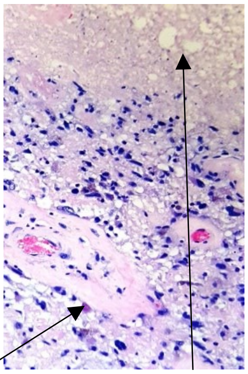
Nuclear atypia and brisk mitotic activity



Perivascular accumulation



Radiation effect



Hyalinized vessels

Radiation Necrosis

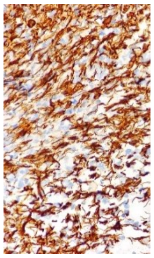
GLIOBLASTOMA, IDH-WILDTYPE (CNS WHO Grade 4)

MORPHOLOGY

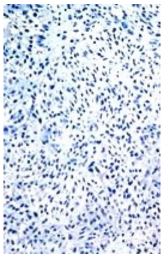
- **Diffusely infiltrating**, **highly cellular** astrocytic neoplasm with **nuclear atypia**, **brisk mitotic activity**, and **at least one** of the following:
  - Microvascular proliferation
  - Pseudopalisading necrosis
  - Polysomy 7 and monosomy 10 (+7/-10)
  - EGFR gene amplification
  - TERT promoter mutation
- Secondary structures of Scherer (indicative of **infiltrative growth**):
  - Perineuronal satellitosis
  - Perivascular accumulation
  - Subpial spread
  - Growth along white matter tracts
- Highly variable histology with regional heterogeneity
- **Specific morphologic patterns**:
  - Epithelioid glioblastoma – associated with BRAF mutations
  - Giant cell glioblastoma – TP53 mutations common
  - Gliosarcoma – GFAP negative sarcomatous components
  - Gemistocytic glioblastoma
  - Small cell glioblastoma
  - Glioblastoma with primitive neuronal component
  - Granular cell glioblastoma

OTHER HIGH YIELD POINTS

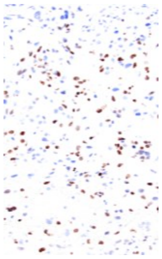
- **Most common** primary CNS malignancy in **adults**
- Typically occurs in **older (>55 years old)** adults
- On imaging, irregularly shaped with ring-shaped enhancement; can grow along the corpus callosum into the other hemisphere ("**butterfly glioma**")
- By definition**, IDH-wildtype** and **H3-wildtype**
- Treatment includes gross total resection followed by radiation and alkylating chemotherapy
- MGMT promoter methylation predicts responsiveness to alkylating chemotherapy agents (i.e., temozolomide)
- IHC: variably positive for GFAP and Olig2; high Ki67 (>15-20%); nuclear ATRX usually retained
- Dismal prognosis, median overall survival ~15 months



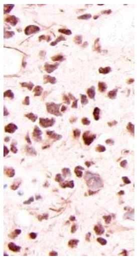
GFAP



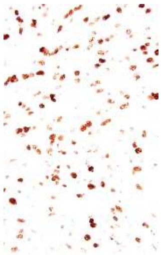
IDH1 R132H



p53



ATRX



Ki67

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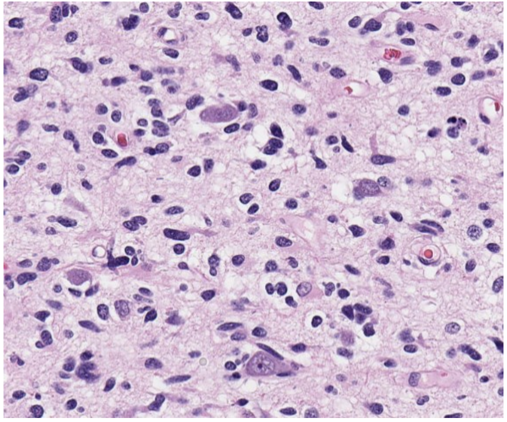
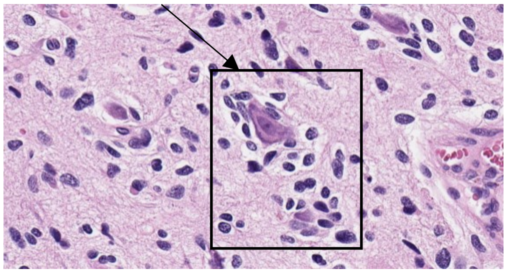
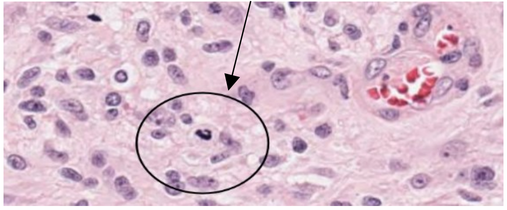
Well-differentiated astrocytic cells (grade 2)



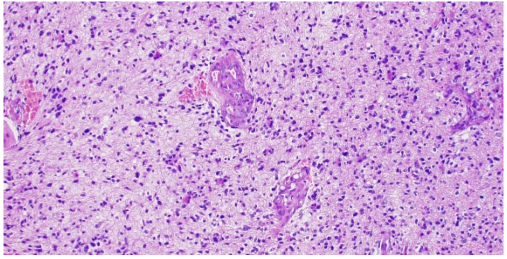
Perineuronal satellitosis



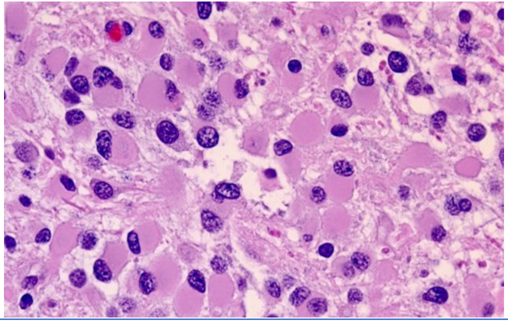
Increased cellularity and mitoses (grade 3)



Microvascular proliferation (grade 4)



Gemistocytic morphology



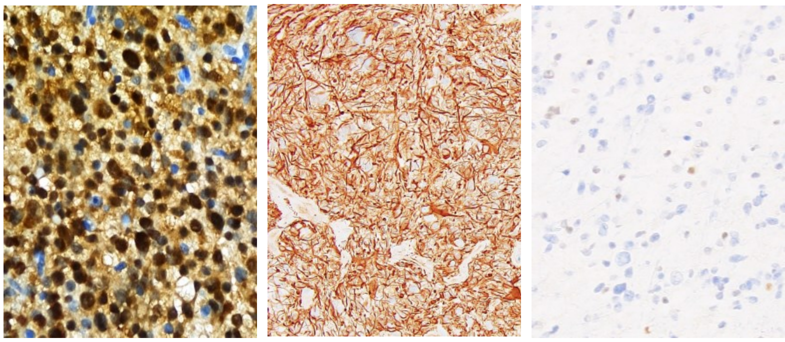
ASTROCYTOMA, IDH-MUTANT (CNS WHO Grade 2-4)

MORPHOLOGY

- **Diffusely infiltrating**, astrocytic neoplasm with a **mutation in either *IDH1* or *IDH2* and intact chromosomes 1p and 19q**
- Secondary structures of Scherer (indicative of **infiltrative growth**, see above)
- Features that **favor neoplastic-type atypia over reactive atypia:**
  - Increased nuclear size and nuclear contour irregularity
  - Hyperchromasia and irregular chromatin distribution
  - Clustering of atypical cells, hypercellular
- Grade 2: well-differentiated fibrillary cells with all of the following:
  - Mild to moderate cellularity and nuclear atypia
  - **Lacking significant mitotic activity**
  - Negative for CDKN2A/B homozygous deletion
- Grade 3: all of the following:
  - Moderate to marked cellularity with increasing nuclear atypia
  - **Brisk mitotic activity**
  - **Negative for CDKN2A/B** homozygous deletion
- Grade 4: increased cellularity and mitotic activity with at least one of the following (substantial **histologically overlap with glioblastoma**, IDH-wildtype):
  - Microvascular proliferation
  - Pseudo palisading necrosis
  - **CDKN2A/B homozygous deletion**

OTHER HIGH YIELD POINTS

- By 2021 WHO, the terms "Diffuse," "Anaplastic," and "Glioblastoma" are no longer applied to IDH-mutant gliomas
- Young adults, commonly present with new onset seizure
- Most commonly found **supratentorially, usually frontal lobes**
- **IDH1 R132H mutation** most common (immunostain available)
- IDH1/2 gene sequencing may be necessary to identify non-canonical IDH mutations
- **Mutations in ATRX** (loss of nuclear immunostaining) and **TP53** (strong nuclear p53 expression) are common
- CDKN2A/B homozygous deletion is strongly associated with poor prognosis and diagnostic of grade 4, even without high-grade histology

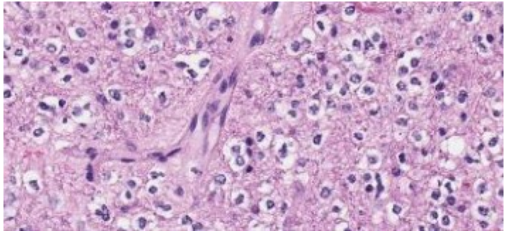


IDH1 R132H GFAP ATRX (loss)

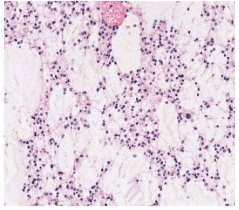
Path Presenter

PP link PP link

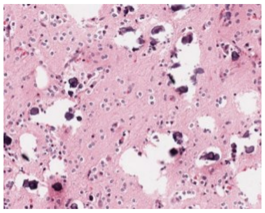
Perinuclear halos (“fried egg” appearance)



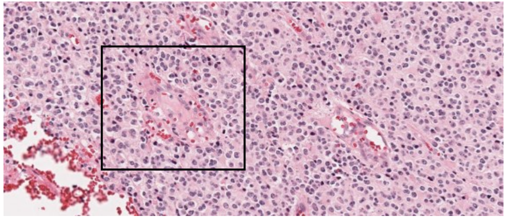
Microcystic change



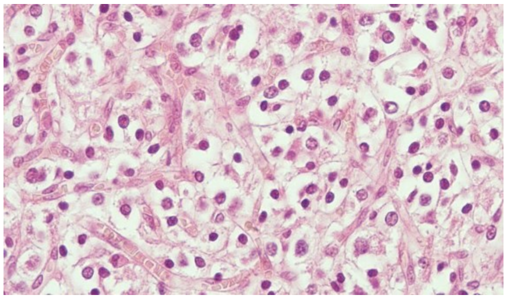
Microcalcifications



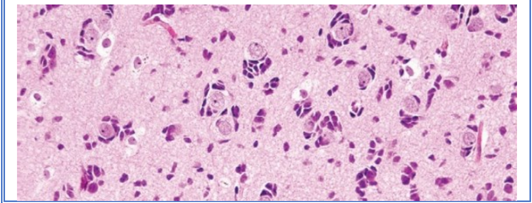
Microvascular proliferation (grade 3)



Chicken wire vasculature



Perineuronal satellitosis



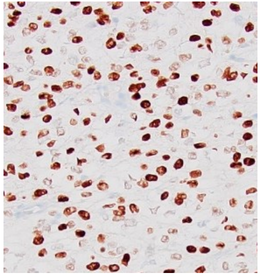
OLIGODENDROGLIOMA, IDH-MUTANT AND 1p/19q-CODELETED (CNS WHO Grade 2-3)

MORPHOLOGY

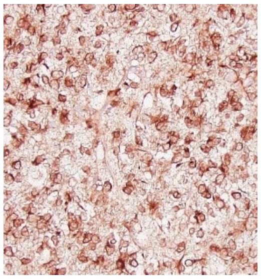
- Diffusely infiltrating glial neoplasm with a **mutation in either IDH1 or IDH2** and **co-deletion of chromosomes 1p and 19q**
- Monomorphic, round nuclei with nuclear halos (“**fried eggs**” – formalin fixation artifact and will not see on frozen section or smear preparation)
- **Microcalcifications and cystic degeneration** are common
- **Chicken wire vasculature**
- Grade 2: All of the following:
  - Moderate cellularity with **low mitotic activity**
  - **Absence of microvascular proliferation and necrosis**
- Grade 3: **at least one** of the following:
  - Brisk **mitotic** activity
  - **Microvascular proliferation**
  - **Pseudo palisading necrosis**

OTHER HIGH YIELD POINTS

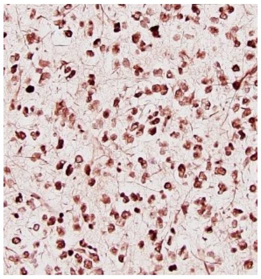
- **Young adults**; commonly present with new onset seizure
- Rare in children, though other pediatric tumors might display “oligo-like” histology
- Most commonly found **supratentorially, usually frontal lobes**
- Prolonged survival compared to other adult-type diffuse gliomas
- **Recurrence and malignant progression** occur but usually at a **slower** rate compared to IDH-mutant astrocytoma and IDH-wildtype glioblastoma
- IHC: (+) IDH1 R132H mutation specific antibody, **Olig2**; **ATRX nuclear expression retained** and **p53 expression weak** (both wildtype patterns), **variable GFAP**
- Frequent **TERT** promoter mutations



Olig2



IDH1 R132H



ATRX (retained)

Path Presenter

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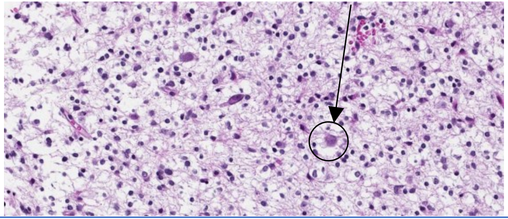
PEDIATRIC-TYPE & INFANT-TYPE DIFFUSE GLIOMAS

Diffuse infiltration with entrapped neurons

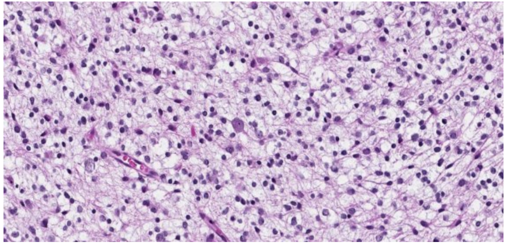


DIFFUSE MIDLINE GLIOMA, H3 K27-ALTERED (CNS WHO Grade 4)

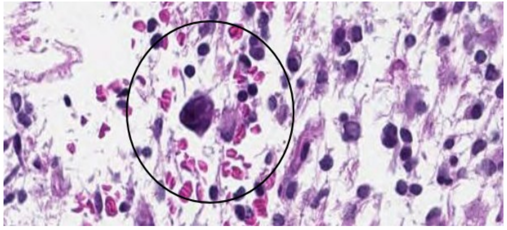
MORPHOLOGY

- **Diffusely infiltrating midline glioma with H3 K27M alteration**
- Usually lacks perivascular or perineuronal satellitosis
- Tumor cells usually **small and monomorphic**, but pleomorphism can be seen
- Mitotically active
- Microvascular proliferation and necrosis can be seen but are not necessary for the diagnosis or grade 4 designation

Small monomorphic cells



Pleomorphism



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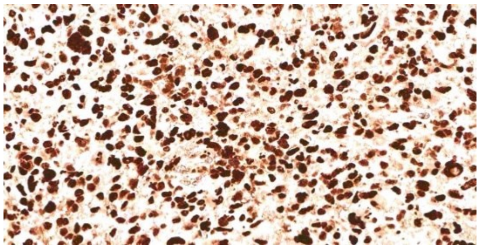
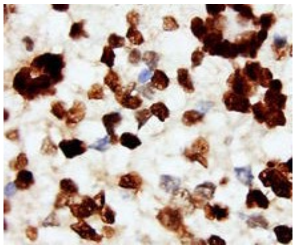
OTHER HIGH YIELD POINTS

- **Usually in children** but can occur in adults
- Midline structures can include the thalamus, hypothalamus, brainstem (most common), cerebellum, and spinal cord
- **Poor prognosis (<2 years)**
- IHC: (+) **H3 K27M mutation-specific antibody**, GFAP, Olig2; loss of H3K27me3 nuclear expression
- Diagnostic molecular features: **H3 K27M (most common),** H3 K27I, EGFR mutation/amplification, EZHIP overexpression, or methylation profile of diffuse midline glioma
- **TP53 and/or ATRX mutations** are occasionally seen

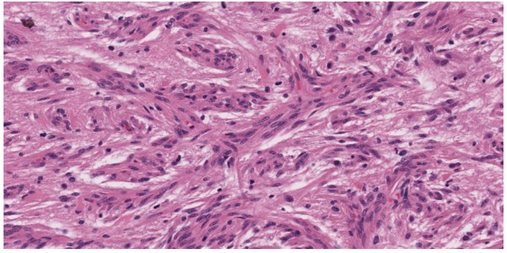


H3 K27M

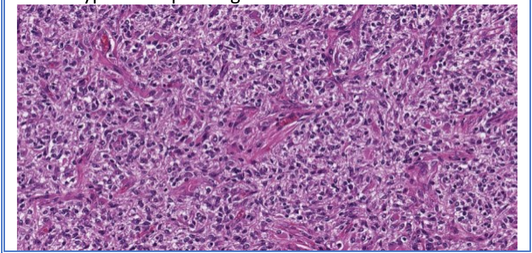


p53

Angiocentric glioma



Infant-type hemispheric glioma



OTHER PEDIATRIC-TYPE DIFFUSE GLIOMAS

DIFFUSE LOW-GRADE GLIOMAS

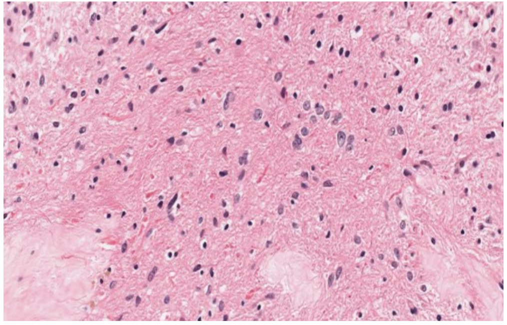
- Diffuse astrocytoma, **MYB- or MYBL1-altered**
  - Hypocellular proliferation of bland astrocytic cells
- **Angiocentric** glioma
  - Uniform spindled cells arranged around blood vessels
  - Frequent MYB-QKI fusion
- **Polymorphous low-grade** neuroepithelial tumor of the young (PLNTY)
  - Oligo-like cells and numerous calcifications
  - IHC: (+) CD34, diffuse
- Diffuse low-grade glioma, MAPK pathway altered

DIFFUSE HIGH-GRADE GLIOMAS

- Diffuse hemispheric glioma, **H3 G34-altered**
  - Glioblastoma-like histology
  - H3 G34R/V mutations most common
- **Infant type hemispheric glioma**
  - Alterations in NTRK family genes or ROS1, ALK, or MET
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

CIRCUMSCRIBED ASTROCYTIC GLIOMAS

Compact zone with Rosenthal fibers

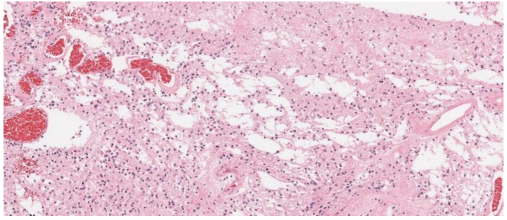


PILOCYTIC ASTROCYTOMA (CNS WHO Grade 1)

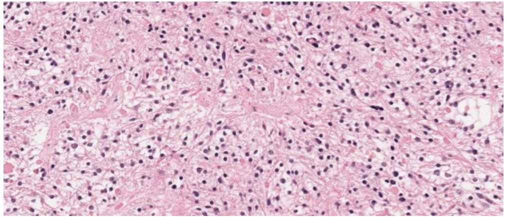
MORPHOLOGY

- Astrocytic neoplasm with **biphasic morphology**:
  - **Compact zone** with bipolar piloid cells and Rosenthal fibers
  - **Loose zone** with microcysts, myxoid background, and eosinophilic granular bodies (EGBs)
- Can have "oligo-like" histology with round nuclei & perinuclear halos
- Low to moderate cellularity
- **Multinucleated cells** with **horseshoe-shaped nuclear clusters** ("pennies-on-a-plate")
- **Glomeruloid microvascular proliferation** is often present and does NOT indicate aggressive behavior

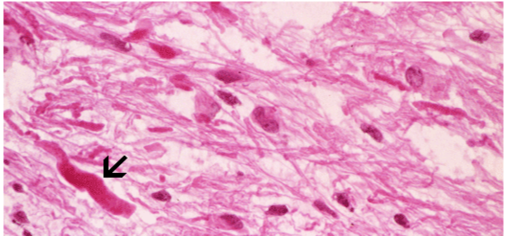
Loose zone with microcysts



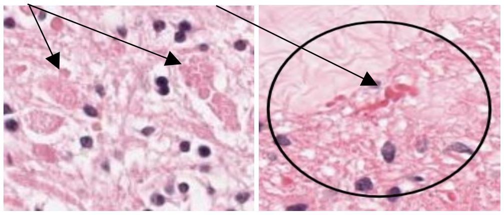
Bipolar cells in fibrillary (piloid) background



Rosenthal fibers and piloid background



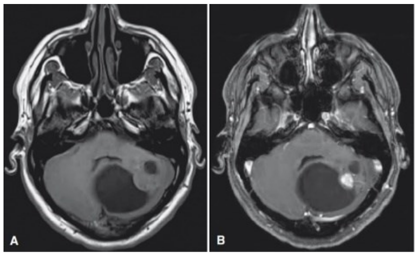
EGBs and Rosenthal fibres



- Degenerative changes: calcifications, hyalinized blood vessels, hemorrhage
- **Minimal mitotic** activity
- **Pilomyxoid astrocytoma**
  - ➢ Subtype of pilocytic astrocytoma with monomorphic piloid cytology, **diffuse myxoid background**, and **increased cellularity**
  - ➢ Prominent **angiocentric** distribution of tumor cells
  - ➢ Generally, **lacks** Rosenthal fibers and eosinophilic granular bodies
  - ➢ Tumor of **infancy,** occurs in **hypothalamic** region
  - ➢ Higher rate of **recurrence** and more likely **CSF dissemination**
- Pilocytic astrocytoma with histologic features of anaplasia
  - ➢ Tumors with morphologic features of pilocytic astrocytoma but also with **brisk mitotic activity**
  - ➢ More common in adults
  - ➢ “High-grade astrocytoma with piloid features” is a diagnosis for astrocytomas showing a distinct methylation profile

OTHER HIGH YIELD POINTS

- **Most common glioma in children**
- **Cerebellum** is the most common location; other midline structures can also be involved (optic pathway, brainstem, etc.)
- Circumscribed and **slow growing**
- **Curable** if surgical excision is possible
- IHC: (+) GFAP, Olig2; low Ki67
- Alterations in MAPK pathway, **KIAA1549-BRAF fusion most common**
- Tumors located along the optic pathway are associated with NF1

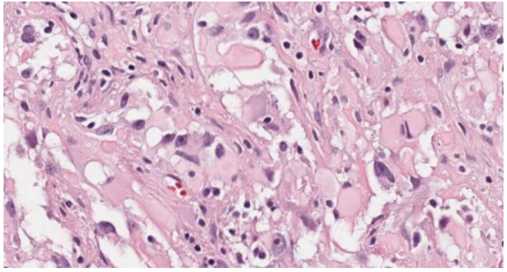


MRI: Well-circumscribed cyst with enhancing mural nodule in the cerebellum, T1 weighted MRI without (left) and with (right) contrast

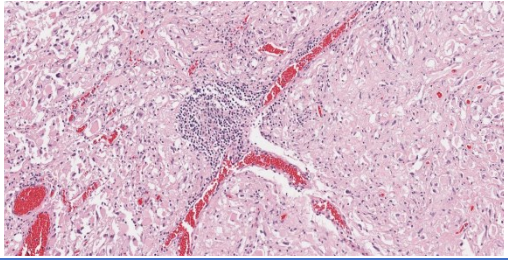
Path Presenter

PP link PP link

Large, pleomorphic lipidized cells



Perivascular lymphocytes



PLEOMORPHIC XANTHOASTROCYTOMA (CNS WHO Grade 2-3)

MORPHOLOGY

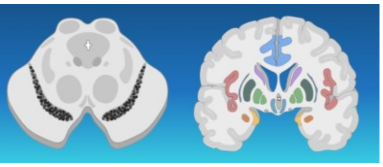
- Astrocytic tumor with **large, pleomorphic, and frequently multinucleated spindled and lipidized cells**
- **Solid, non-infiltrative** growth pattern
- Frequent intranuclear inclusions and **prominent nucleoli**
- Dense **reticulin network** (reticulin fibers surrounding individual tumor cells), **eosinophilic granular bodies**, and **perivascular lymphocytes**

OTHER HIGH YIELD POINTS

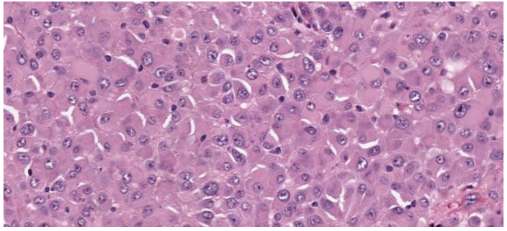
- **Children and young adults,** superficial location in cerebral hemispheres, usually the **temporal lobe**
- **BRAF V600E mutation** (or other MAPK pathway alteration) and **CDKN2A/B homozygous deletion** are characteristic
- **Grade 2: < 5 mitoses** / 10 high power fields
- **Grade 3: ≥ 5 mitoses** / 10 high power fields

Path Presenter

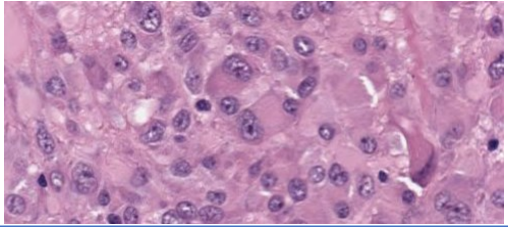
11. NEUROPATHOLOGY



Large, plump gemistocytic astrocytes



Ganglion like cells, multinucleation



SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA, CNS WHO GRADE 1)

MORPHOLOGY

- Benign, slow-growing, well-circumscribed tumor
- **Large gemistocytic astrocytes** with abundant **pink, glassy cytoplasm**
- Frequently with **giant, ganglion-like cells** with **prominent nucleoli**
- Pleomorphism and multinucleation are common
- Arranged in fascicles, sheets, and nests

OTHER HIGH YIELD POINTS

- Typically located along walls of **lateral ventricles**
- Commonly present with seizures before 20 years old
- Strong association with **tuberous sclerosis**
- Good prognosis with total resection

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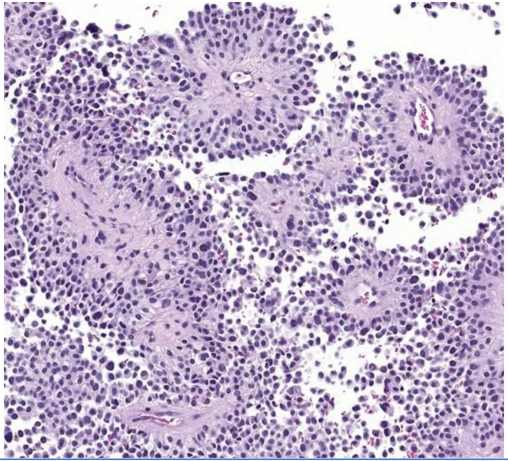
Astroblastic pseudorosettes



ASTROBLASTOMA, MN1-ALTERED

MORPHOLOGY

- **Circumscribed glial neoplasm** with round, cuboidal, or columnar cells
- Variable **papillary** or **perivascular** growth patterns ("**astroblastic pseudorosettes**") with **hyalinized blood vessels**
- Mitotic activity highly variable, and some cases with necrosis and microvascular proliferation (CNS WHO grade not currently defined)

OTHER HIGH YIELD POINTS

- Located in cerebral hemispheres of **children and young adults**
- IHC: (+) GFAP, Olig2, **EMA** (diffuse, membranous, dot-like, or ring-like)
- Defined by presence of **MN1 alteration**, usually gene fusion (**MN1-BEND2 fusion** most common)

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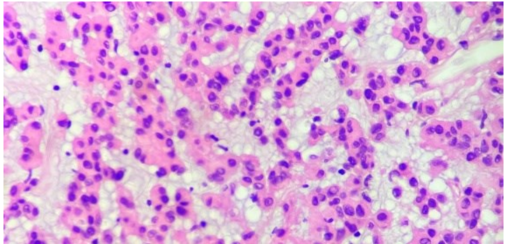
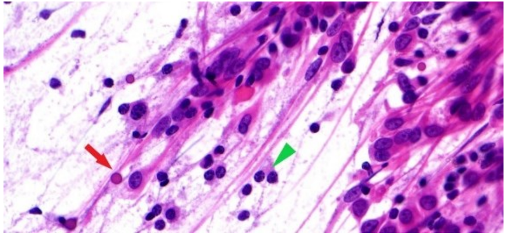
Chords of neoplastic cells in variable mucinous stroma



Courtesy: Dr. Simon Roy, MD (@Simon Roy, MD)



Courtesy: Dr. Mireille Bitar, M.D. (@bitar_mireille)

CHORDOID GLIOMA (CNS WHO Grade 2)

MORPHOLOGY

- Well-circumscribed tumor with **clusters/chords of epithelioid neoplastic glial cells**
- Solid with variably mucinous stroma
- Mitoses rare to absent
- Lymphoplasmacytic infiltrate (green arrowhead) with numerous Russell bodies (red arrow)

OTHER HIGH YIELD POINTS

- Stereotypical location within the **third ventricle**
- **PRKCA D463H mutation**
- Rare (< 0.1% of primary brain tumors)
- Most frequently in adults
- IHC: positive GFAP (strong, diffuse), **TTF1**, CD34

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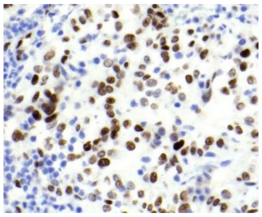
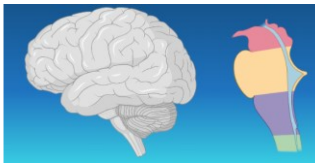


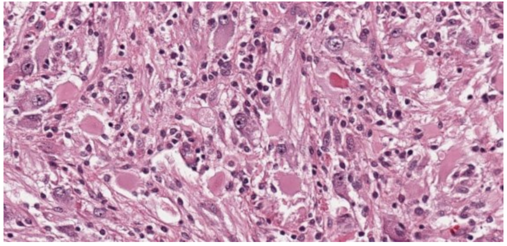
TTF-1



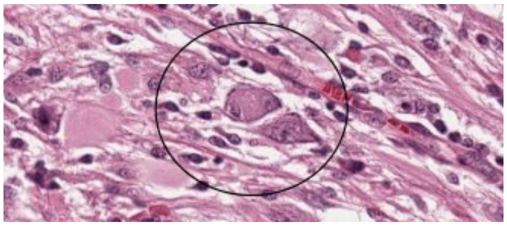
11. NEUROPATHOLOGY

NEURONAL & GLIONEURONAL TUMORS

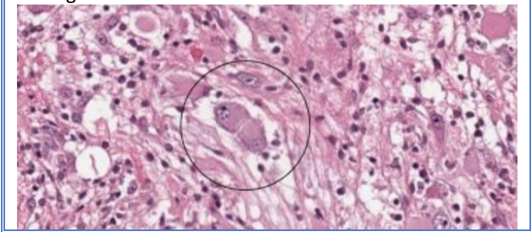
Mixture of glial and ganglion-like cells



Binucleation



Kissing cells



GANGLIOGLIOMA / GANGLIOCYTOMA (CNS WHO Grade 1)

MORPHOLOGY

- Mixture of **glial** and **ganglion-like neoplastic cells** (ganglioglioma) or **purely ganglion-like** cells (gangliocytoma)
- Dysplastic ganglion cells with **dysmorphic neuronal features**, including **binucleation** or abnormal clustering ("**kissing cells**")
- Neoplastic glial cells may **resemble low-grade astrocytoma**
- Intracortical, circumscribed, cystic growth
- Eosinophilic granular bodies, calcifications, lymphoid infiltrates, and prominent capillary networks
- Mitotic activity **low to absent**

OTHER HIGH YIELD POINTS

- **Children and young adults**
- **Temporal lobe** most common
- **MAPK** pathway alterations (BRAF V600E in ~25% of cases)
- **Excellent outcome**
- IHC: neuronal component positive for **neuronal markers** (i.e., MAP2, neurofilament, chromogranin) and **negative for NeuN**; CD34-positive ramified cells
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease): rare, benign cerebellar lesion associated with Cowden Syndrome

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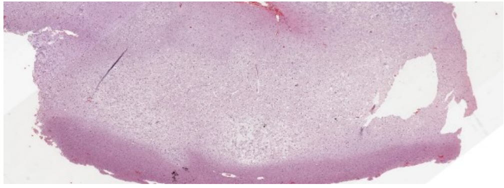
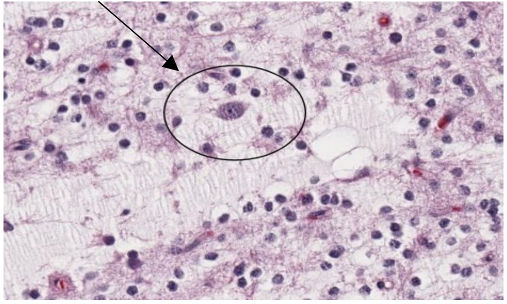
Intracortical nodular growth



Floating neuron, mucin pools, oligo-like cells



DYSEMBRYOBLASTIC NEUROEPITHELIAL TUMOR (DNT, CNS WHO Grade 1)

MORPHOLOGY

- Columns of small, round, monotonous cells ("**oligo-like**") oriented perpendicular to the cortical surface and lining bundles of axons (specific glioneuronal element)
- Non-neoplastic **neurons "floating"** in mucin pools
- Nodular/lobulated architecture with sharply defined margin
- Sometimes associated with adjacent cortical dysplasia

OTHER HIGH YIELD POINTS

- **Children and young adults**; often present with **seizures**
- Cortical, most common in **temporal lobe**
- **Excellent outcomes**
- IHC: "oligo-like" cells express **Olig2 but not GFAP**
- Characterized by **activating mutations of FGR1**
- Histopathologic diagnosis can be challenging on small biopsy specimens

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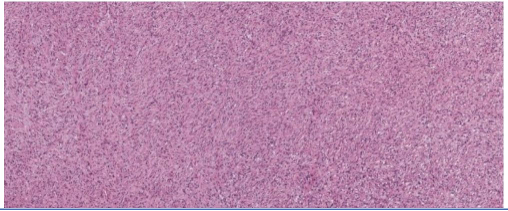
Streams of neoplastic cells

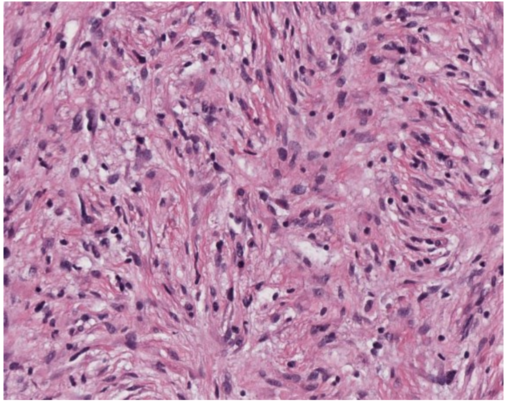


DESMOPLASTIC INFANTILE ASTROCYTOMA (DIA) / GANGLIOGLIOMA (DIG) (CNS WHO Grade 1)

MORPHOLOGY

- Prominent **desmoplastic stroma** with a **neoplastic population of astrocytes** (DIA), ± **mature neuronal elements** (DIG)
- Often with foci of undifferentiated **embryonal-like** cells
- Sharply demarcated from adjacent cortex

Fibroblast-like cells in collagen matrix



- **Leptomeningeal involvement** is common
- **Reticulin-rich, fibers** surrounding nearly every tumor cell
- **Calcifications** common
- **Limited mitotic** activity, primarily limited to embryonal-like foci

OTHER HIGH YIELD POINTS

- Rare neoplasm of **early childhood**, located in cerebral hemispheres
- Often large and cystic
- IHC: (+) GFAP; ganglion cells (if present) express synaptophysin, neurofilament, NeuN
- **MAPK** pathway alterations, most commonly fusions or mutations of BRAF or RAF1

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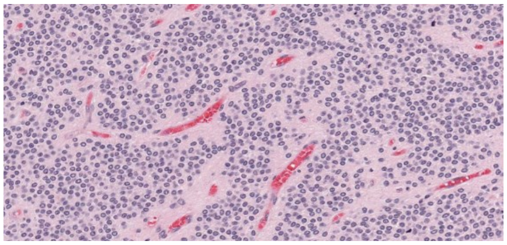
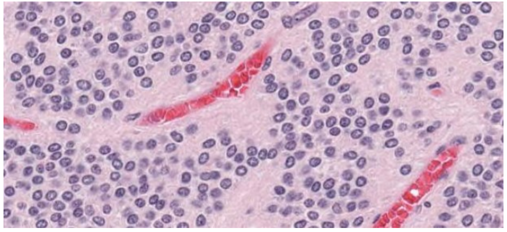
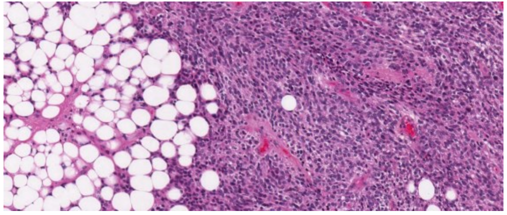
Sheets of uniform cells



Round cells with speckled chromatin



Cerebellar liponeurocytoma



CENTRAL NEUROCYTOMA, EXTRAVENTRICULAR NEUROCYTOMA, AND CEREBELLAR LIPONEUROCYTOMA (CNS WHO Grade 2)

MORPHOLOGY

- Sheets of **uniform round cells** with **salt-and-pepper chromatin**
- **Perinuclear halos** ("oligo-like") and calcifications are common
- Mitotic activity is **low**
- Wider morphologic spectrum in extra ventricular neurocytoma
- **Focal lipoma-like changes** seen in cerebellar liponeurocytoma

OTHER HIGH YIELD POINTS

- Young adults
- **Central neurocytoma:**
  - ➢ Lateral ventricles most common
  - ➢ No recurrent molecular alterations
- **Extra ventricular neurocytoma:**
  - ➢ Can occur almost anywhere in the CNS
  - ➢ Commonly with FGFR2-TACC1 gene fusions
- **Cerebellar liponeurocytoma:**
  - ➢ Located in cerebellum
  - ➢ Recurrent focal losses of chromosomes 14 and 2p
  - ➢ Lipomatous changes may be absent at recurrence
- IHC: (+) synaptophysin (most reliable), NeuN, MAP2, TTF1; (-) chromogranin, neurofilament

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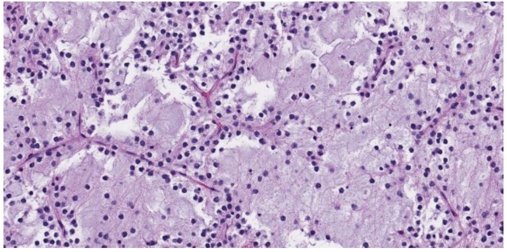
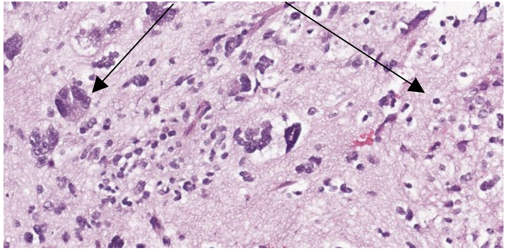
Myxoid glioneuronal tumor



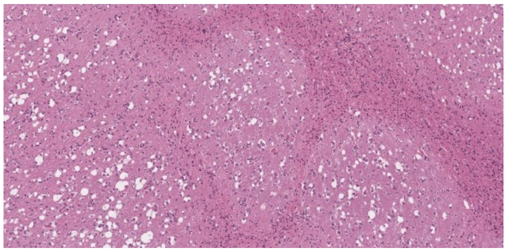
OTHER NEURONAL AND GLIONEURONAL TUMORS

- **Papillary glioneuronal tumor (PGNT)**
  - ➢ Prominent **pseudopapillary architecture** with **cuboidal glial cells around hyalinized blood vessels**
  - ➢ Intervening collections of neurocytes in a neuropil background
  - ➢ Fibrillary or microcystic background
  - ➢ Located in cerebral hemispheres (near **lateral ventricles**) of young adults
  - ➢ Frequent **SLC44A1-PRKCS** gene fusion
- **Rosette-forming glioneuronal tumor (RGNT)**
  - ➢ Uniform neurocytes forming rosettes and/or perivascular pseudorosettes

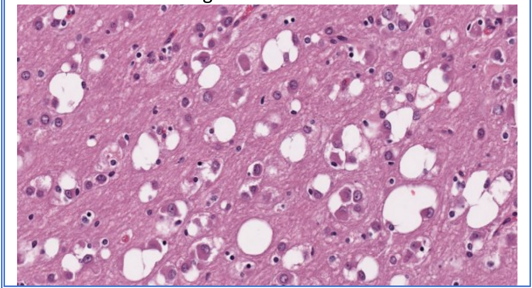
DGONC: nuclear clusters and oligo-like cells



MVNT: multinodular architecture



MVNT: vacuolar change

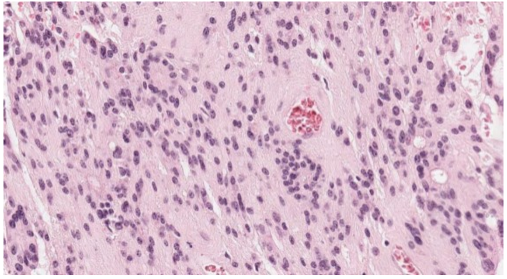


- Glial component resembling pilocytic astrocytoma
- Most commonly in fourth ventricle of young adults
- FGF1 mutation with frequent co-occurring PIK2CA and/or NF1 alterations

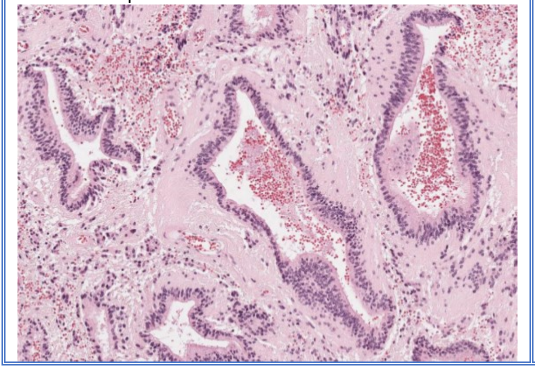
- **Myxoid glioneuronal tumor (MGNT)**
    - Glioneuronal tumor composed of **"oligo-like" cells** in a prominent **myxoid** background (resembles DNT)
    - Most commonly in septum pellucidum of children and young adults
    - Recurrent **PDGFRA** mutations (K385L and K385I)
- **Diffuse leptomeningeal glioneuronal tumor (DLGNT)**
    - Monomorphic "oligo-like" cells with desmoplastic/myxoid change and widespread leptomeningeal growth
    - Rare tumor in children
    - 1p deletion and MAPK pathway alteration (**KIAA1549-BRAF fusion** most common)
- **Diffuse glioneuronal tumor with oligodendroglioma-like histology and nuclear clusters (DGONC)**
    - Neuroepithelial tumor composed of small to medium-sized **oligo-like** cells and scattered **multinucleated** cells with nuclei arranged on periphery ("pennies-on-a-plate) or **in clusters**
    - Rare tumor, predominantly in **children**
    - Distinct methylation profile and frequently monosomy 12
- **Multinodular and vacuolating neuronal tumor (MVNT)**
    - Monomorphic neuronal elements arranged in discrete, pale nodules with vacuolating changes within tumor cells and matrix
    - Highly characteristic on MRI as stable, hyperintense, non-enhancing nodules in deep cortex and superficial white matter
    - Young adults, benign, good prognosis

EPENDYMAL TUMORS

Uniform round cells in fibrillary matrix



Perivascular pseudorosettes



EPENDYMOMA (CNS WHO Grades 2-3)

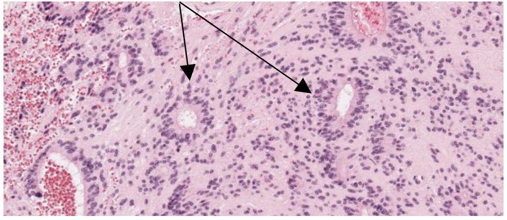
MORPHOLOGY

- Circumscribed glioma (not diffusely infiltrative)
- Uniform **small cells with round nuclei** and speckled chromatin
- **Fibrillary matrix**
- Characteristic **perivascular pseudorosettes**
- **True ependymal rosettes** found in minority of cases
- High-grade features seen in more aggressive tumors
    - Brisk mitotic activity and microvascular proliferation are more prognostic than atypia and necrosis
- **Clear cell** pattern more common in supratentorial ependymoma
- **Papillary** pattern more common in posterior fossa ependymoma
- **Tanycytic** pattern (spindled cells in fascicles) more common in spinal ependymoma

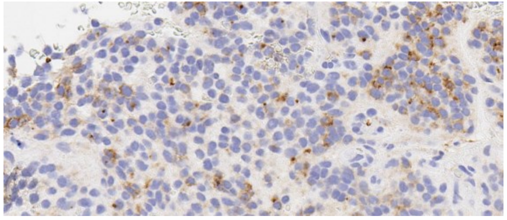
OTHER HIGH YIELD POINTS

- Classification based on anatomic location, histomorphology, and molecular features
- Histological grade (CNS WHO grades 2 and 3) does not consistently correlate with tumor behavior and prognosis
- IHC: (+) GFAP, **EMA (peri-nuclear dot-like pattern)**
- Spinal ependymoma generally shows loss of chromosome 22 and is associated with Neurofibromatosis type 2 (NF2)

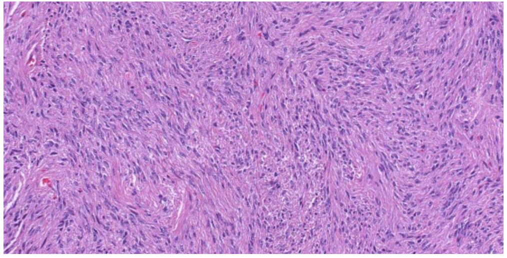
True ependymal rosettes



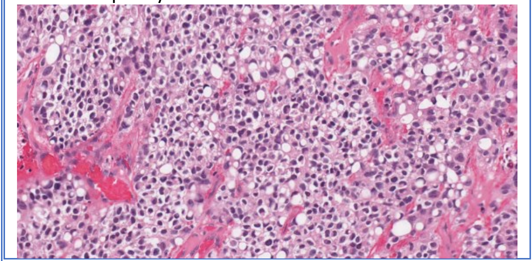
EMA: perinuclear dot-like pattern



Tanycytic ependymoma



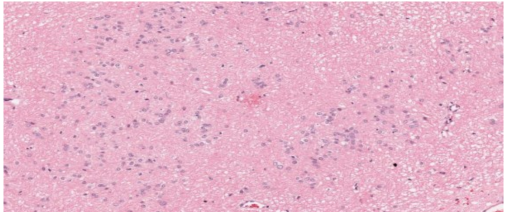
Clear cell ependymoma



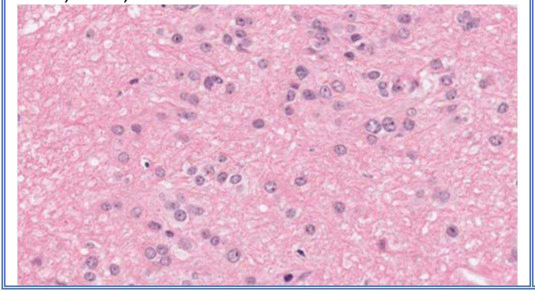
EPENDYMOMA CLASSIFICATION	
SUPRATENTORIAL EPENDYMOMA	- **ZFTA (C11orf95) FUSION-POSITIVE** All ages Intermediate prognosis IHC (+) L1CAM CDKN2A/B loss Chromothripsis - **YAP1 FUSION-POSITIVE** Infants and children Good prognosis
POSTERIOR FOSSA EPENDYMOMA	- **GROUP A (PFA)** Infants and children Poor prognosis EZHIP or H3 K27M mutation IHC: loss of H3 K27me3 nuclear staining Chromosome 1q gain - **GROUP B (PFB)** Children < adults Good prognosis IHC: retained nuclear H3 K27me3 Chromosomal instability
SPINAL EPENDYMOMA	- **SPINAL EPENDYMOMA** Adults Intermediate prognosis NF2 mutations Loss of chromosome 22 Absence of MYCN amplification - **MYCN-AMPLIFIED** Children and adults Poor prognosis Usually cervical or thoracic spinal cord High-grade histology usually present Frequent CSF dissemination

Path Presenter

Clusters of cells in abundant fibrillary matrix



Small, bland, round to oval nuclei



SUBEPENDYMOMA (CNS WHO Grade 1)

MORPHOLOGY

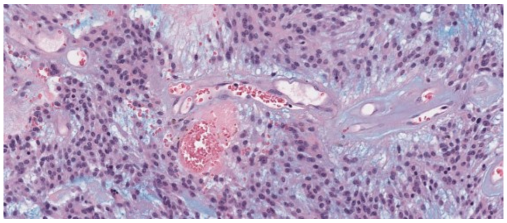
- **Clusters of mostly bland cells** embedded in **abundant fibrillary matrix**
- Frequently with microcystic change, sometimes calcified
- **Rare pseudorosettes**
- No significant mitotic activity or atypia

OTHER HIGH YIELD POINTS

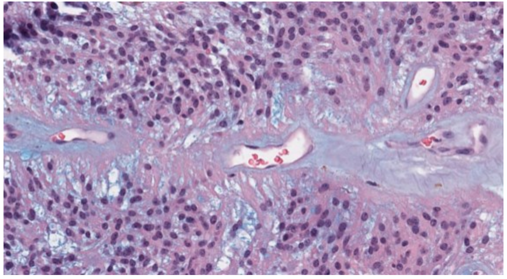
- Adults, slow growing, exophytic, **intraventricular**
- Often incidentally found by neuroimaging or at autopsy
- Can be found in supratentorial, posterior fossa, or spinal compartments (each with a unique methylation profile)
- Fourth ventricle and lateral ventricles are most common locations
- IHC: (+) GFAP, **focal dot-like EMA pattern**
- Good prognosis

Path Presenter

Pseudorosettes with mucoid material



Bland cuboidal cells with radial arrangement



MYXOPAPILLARY EPENDYMOMA (CNS WHO Grade 2)

MORPHOLOGY

- Elongated cuboidal cells arranged in r**adial patterns around hyalinized, mucoid, fibrovascular core**s
- Myxoid material highlighted with **PAS and Alcian blue**
- Microcysts
- Spindled cells and **fascicular growth** are common
- Low mitotic activity

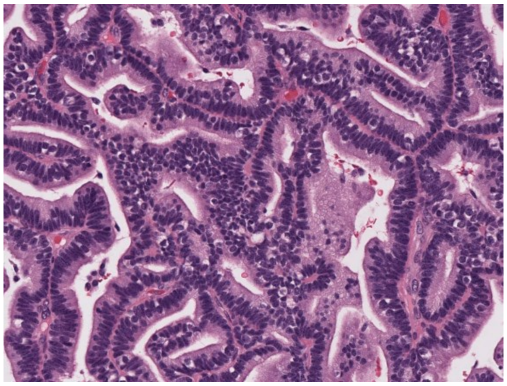
OTHER HIGH YIELD POINTS

- Young adults
- Arise almost exclusively in the region of the **lower spinal cord:** conus medullaris, cauda equina, filum terminale
- Relatively favorable prognosis but difficult to resect; recurrence and CSF dissemination are common
- IHC: (+) GFAP; **(-) Olig2, EMA**

Path Presenter

CHOROID PLEXUS TUMORS

Delicate fibrovascular fronds



CHOROID PLEXUS PAPILLOMA (CNS WHO Grade 1)

MORPHOLOGY

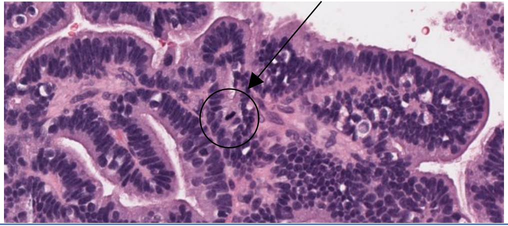
- Delicate **fibrovascular fronds** covered by **single layer of cuboidal to columnar epithelium**
- Round to oval, **basal, monomorphic** nuclei
- **<2 mitoses** per 10 high power field

OTHER HIGH YIELD POINTS

- All ages but more common in children, usually **lateral ventricle**
- IHC: (+) cytokeratins (**CK7+** CK20-), Kir7.1, S100
- Curable by surgical resection

Path Presenter

Increased cellularity and focal mitotic activity



ATYPICAL CHOROID PLEXUS PAPILLOMA (CNS WHO Grade 2)

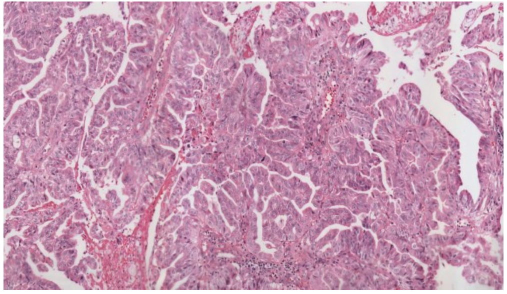
MORPHOLOGY

- Morphologically resembles choroid plexus papilloma but with increased mitotic activity (**≥2 mitoses per 10** high power fields)
- Often with increased cellularity, nuclear **pleomorphism**, **solid growth**, and/or **necrosis**

OTHER HIGH YIELD POINTS

- More likely to recur but still relatively good prognosis

Blurring of papillary pattern



CHOROID PLEXUS CARCINOMA (CNS WHO Grade 3)

MORPHOLOGY

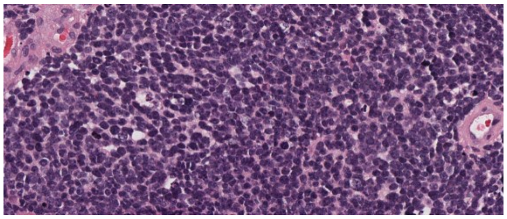
- Frankly malignant epithelial neoplasm with at least 4 of the following:
    1. Brisk mitotic activity (**>5 mitoses per 10** high power fields)
    2. Increased **cellular density**
    3. Nuclear **pleomorphism**
    4. Blurring of papillary pattern with poorly formed **sheets of tumor cells**
    5. **Necrosis**

OTHER HIGH YIELD POINTS

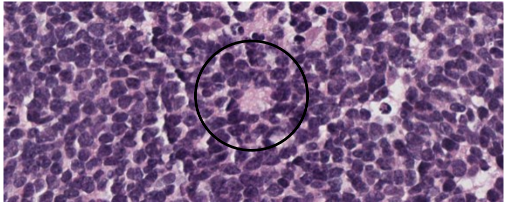
- **Frequently invades** neighboring brain and metastasized via CSF
- **TP53 mutations** common and is associated with **Li Fraumeni Syndrome**

EMBRYONAL TUMORS

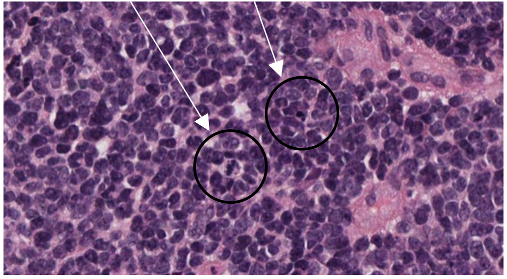
Small round blue cell tumor



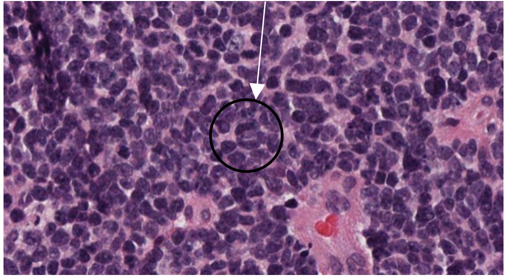
Homer-Wright rosette



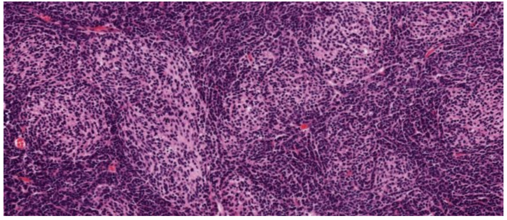
Numerous mitoses and apoptoses



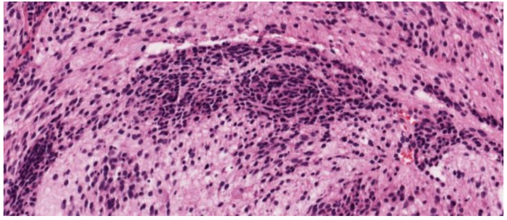
Nuclear molding and cell wrapping



Desmoplastic/nodular medulloblastoma



Medulloblastoma with extensive nodularity



MEDULLOBLASTOMA (CNS WHO Grade 4)

MORPHOLOGY

- Small, **poorly differentiated** cells with **high N: C ratio**
- Nuclear **molding**
- High **mitotic** index and numerous **apoptotic** cells
- Cytologic and architectural diversity
- **Classic medulloblastoma:**
  - Densely packed small round blue cells, **Homer-Wright** rosettes
  - Arrangement in parallel rows (spongioblastic pattern)
  - Lacks significant reticulin staining
- **Desmoplastic/nodular medulloblastoma:**
  - Nodular, reticulin free zones ("**pale nodules**") surrounded by **densely** packed **small round blue** cells
  - Nodules demonstrate low proliferation and higher expression of **neuronal markers**
  - Internodular areas with small round blue cells demonstrate high proliferation and low expression of neuronal markers
  - **Reticulin rich (desmoplastic) internodular** areas
- **Medulloblastoma with extensive nodularity (MBEN):**
  - Lobular architecture with elongated, reticulin free zones containing small neurocytic cells (NeuN-positive) with a fibrillary background
  - High proliferation index in internodular areas
- **Large cell/anaplastic medulloblastoma:**
  - Marked nuclear **pleomorphism**
  - High **mitotic** index and numerous **apoptotic** bodies
  - **Nuclear molding**, cytoplasmic pseudoinclusions, **cell wrapping**
  - Large cell phenotype with uniformly large cells containing **prominent nucleoli**

OTHER HIGH YIELD POINTS

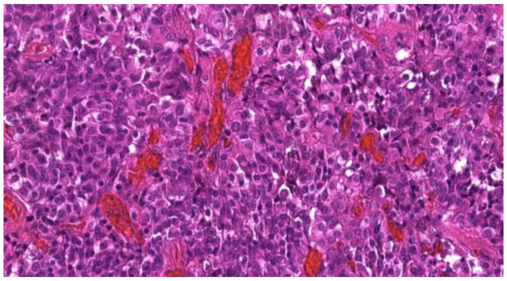
- **Second most common** malignant CNS tumor of **childhood**
- Located in **fourth ventricle** or **cerebellar** parenchyma
- Classification based on combination of molecular and histologic features
- Tumors located in lateral cerebellar hemisphere almost **always SHH-activated**
- IHC: variable expression of nonspecific neural markers (CD56, MAP2, NSE), synaptophysin, NeuN; rare GFAP expression
  - **SHH**-activated tumors: (+) **GAB1, p75-NGFR**
  - Extensive, **strong p53** expression in **TP53 mutant** tumors
  - **NeuN** expression enriched in nodules of **desmoplastic/nodular** medulloblastoma and **MBEN**
  - **Nuclear beta-catenin** expression in **WNT-activated** tumors
- **WNT-activated tumors have excellent response to treatment** and are curable; nearly all with classic histology
- All tumors with **desmoplastic/nodular** and **extensive nodularity** belong to the **SHH-activated** molecular group
- Associated **inherited cancer syndromes**: nevoid basal cell carcinoma/Gorlin syndrome, Li-Fraumeni syndrome, familial adenomatous polyposis, Rubinstein-Taybi syndrome, Nijmegen breakage syndrome, and others

Path Presenter

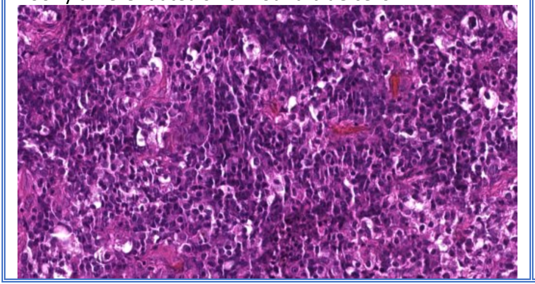
MEDULLOBLASTOMA, MOLECULARLY DEFINED

WNT-activated	10% Childhood, M<F Classic histology Monosomy 6 CTNNB1, DDX3X mutations Germline APC mutations
SHH-activated TP53-wildtype (Subgroups SHH-1 to SHH-4)	20% Infancy/adulthood, M=F **Desmoplastic/nodular histology, occasionally MBEN** PTCH1 deletion; 10q loss PTCH1, SMO, SUFU, ELP1, DDX3X, KMT2D, U1 snRNA mutations Germline PTCH1, SUFU, ELP1 mutations
SHH-activated TP53-mutant (Subgroup SHH-3)	10% Childhood, M>F **Large cell/anaplastic histology** MYCN, GLI2 amplification; 17p loss TP53, DDX3X, U1 snRNA, TERT mutations Germline TP53 mutations
Non-WNT/non-SHH group 3 (Group 3/4 subgroups 1-8)	25% Infancy/childhood, M>F **Classic histology**, occasional large cell/anaplastic histology MYC, MYCN amplification; gain of 1q, 7; loss of 10q, 16q, isodicentric 17q GFI1, FGI1B, SMARCA4, KBTBD4, CTDNEP1, KMT2D mutations Germline BRCA2, PALB2 mutations (rare)
Non-WNT/non-SHH group 4 (Group 3/4 subgroups 1-8)	35% **All age groups**, M>F Classic histology, occasional large cell/anaplastic histology MYCN, OTX2, CDK6 amplification; gain of 7; loss of 8, 11; isodicentric 17q FGI1, FGI1B, PRDM6, KDM6A, ZMYM3, KMT2C, KMT2D, KBTBD4 mutations Germline BRCA2, PALB2 mutations (rare)

Rhabdoid cells



Poorly differentiated small round blue cells



ATYPICAL TERATOID/RHABDOID TUMOR (AT/RT, CNS WHO Grade 4)

MORPHOLOGY

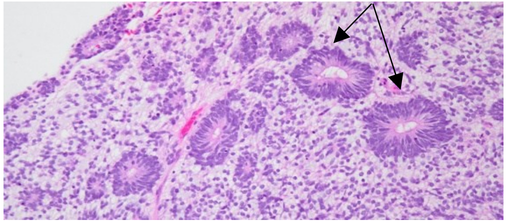
- Variable number of **rhabdoid** cells with **eccentric nuclei** (may only be focally present), vesicular chromatin**, prominent nucleoli**
- Abundant **eosinophilic** cytoplasm
- Numerous **mitoses**, geographic **necrosis**
- **Heterogeneous tumors** with poorly differentiated small round blue cell elements in addition to areas with neuroectodermal, epithelial, and/or mesenchymal differentiation

OTHER HIGH YIELD POINTS

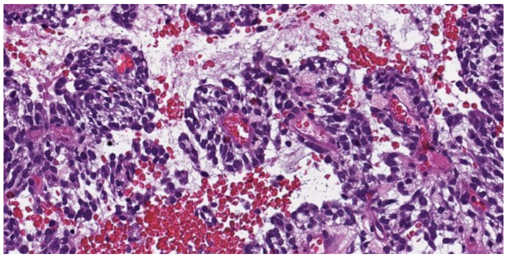
- **Infants and young children**; occur throughout the neuraxis
- IHC: **loss of INI1** (rarely loss of BRG1); (+) EMA, SMA; (+/-) GFAP, synaptophysin, cytokeratin
- Molecular: biallelic inactivation of **SMARCB1** (INI1, most common) or SMARCA4 (BRG1, rare)
- Very aggressive, poor prognosis

Path Presenter

Embryonal tumor with multilayered rosettes (ETMR)



CNS tumor with BCOR ITD



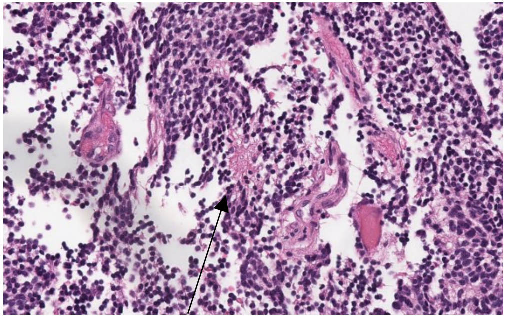
Path Presenter

OTHER CNS EMBRYONAL TUMORS

- **Embryonal tumor with multilayered rosettes (ETMR)**
  - Embryonal cells forming multilayered rosettes
  - High mitotic index, poor prognosis
  - IHC: (+) **LIN28**
  - **C19MC structural alterations** or rarely DICER1 mutation
- **Cribriform neuroepithelial tumor (CRINET)**
  - Highly cellular, non-rhabdoid tumor with cribriform strands and ribbons
  - **Loss of nuclear SMARCB1 (INI1)** expression
  - Characteristic strong EMA expression
- **CNS neuroblastoma, FOXR2-activated**
  - Embryonal tumor with high N: C ratio and poorly differentiated cells
  - Sheets of neurocytic and neuroblastic cells in a neuropil-like matrix; sometimes with focal ganglion cells
  - Necrosis and high mitotic index
  - IHC: (+) Olig2; (+/-) synaptophysin; (-) GFAP
- **CNS tumor with BCOR internal tandem duplication**
  - **Myxoid or microcystic matrix** and branching **capillary network**
  - Ependymoma-like **pseudorosettes** (GFAP-negative)
  - High **mitotic** activity, pseudopalisading **necrosis**
  - Well-demarcated from adjacent brain

PINEAL TUMORS

Uniform, small, mature cells



Pineocytomatous rosette

PINEOCYTOMA (CNS WHO Grade 1)

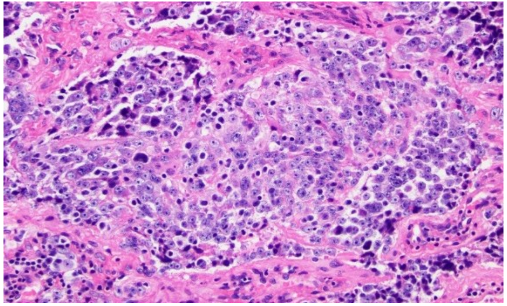
MORPHOLOGY

- Sheet-like growth of **uniform, small, mature cells** (resembling normal pineal cells) with round nuclei and fine chromatin
- Large **pineocytomatous rosettes** (not seen in normal pineal gland)
- Occasional pleomorphic cells with ganglionic differentiation
- Mitoses rare or absent; **low Ki67** (<1%)
- Well demarcated, solid mass without infiltration or dissemination

OTHER HIGH YIELD POINTS

- Rare tumor, adults, exclusively located in **pineal region**
- IHC: (+) **synaptophysin, NSE, neurofilament, CRX**
- **Excellent** prognosis

Lobule of hypercellular, atypical cells



PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION (PPTID, CNS WHO Grade 2-3)

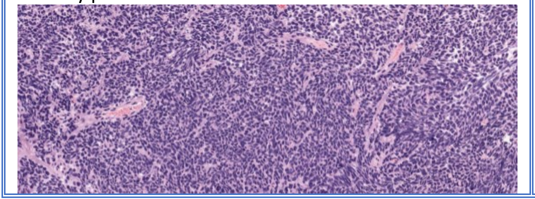
MORPHOLOGY

- Diffuse **sheets or large lobules** of **monomorphic round cells**
- Occasional pleomorphic cells
- **Increased cellularity** compared to pineocytoma
- Mitotic activity low to moderate; **Ki67 elevated (usually >5%)**

OTHER HIGH YIELD POINTS

- **Intermediate** in malignancy between **pineocytoma and pineoblastoma**
- Definite grading criteria remain to be defined, though majority correspond to WHO grade 2

Densely packed small round blue cell tumor

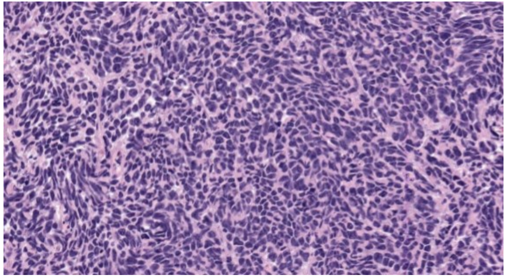


PINEOBLASTOMA (CNS WHO Grade 4)

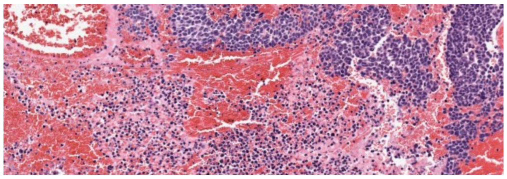
MORPHOLOGY

- Poorly differentiated, **highly cellular** small round blue cell tumor
- **Patternless** sheets of small **immature neuroepithelial cells**
- **High N: C ratio, hyperchromatic**
- Mitoses frequent; **Ki67 markedly elevated (>20%)**
- **Necrosis** is common

High N:C ratio and hyperchromatic nuclei



Tumor necrosis



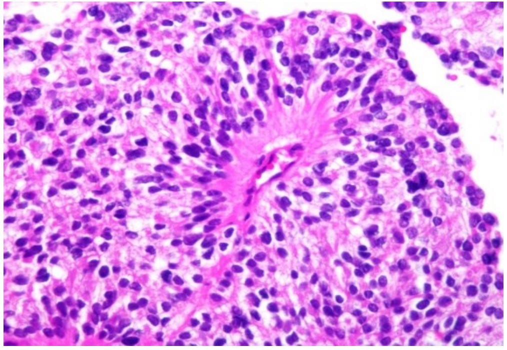
Path Presenter

- Pineocytomatous rosettes are absent but **may encounter Homer-Wright and Flexner-Wintersteiner rosettes**
- PINEAL ANLAGE TUMOR
    - Extremely rare
    - Considered a subtype of pineoblastoma but shares molecular features of other embryonal malignancies
    - **Biphasic** tumor with pineoblastoma-like elements (including melanin containing epithelioid cells) and heterologous ectomesenchymal elements (rhabdomyoblasts, striated muscle, cartilaginous islands, etc.)

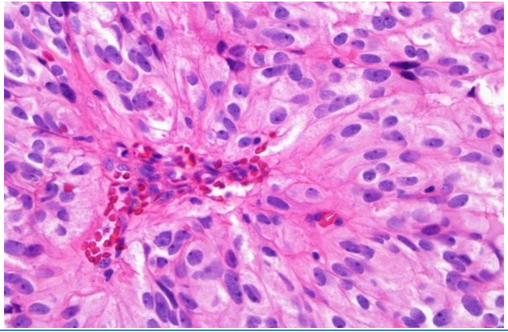
OTHER HIGH YIELD POINTS

- **Children**
- **Invades** adjacent structures and frequently **disseminates through CSF**
- Four molecular subgroups:
    - miRNA processing-altered_1 – associated with DICER1 syndrome
    - miRNA processing-altered_2 – associated with DICER1 syndrome
    - RB1-altered (pineal retinoblastoma) – associated with hereditary retinoblastoma
    - MYC/FOXR2-activated
- Aggressive clinical course

Papillary tumor of the pineal gland

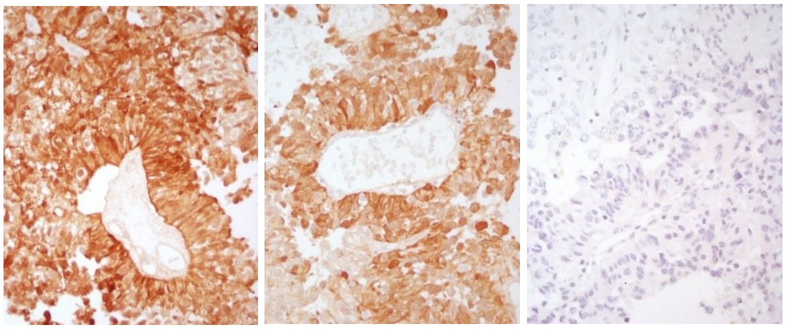


Uniformly round nuclei with stippled chromatin



OTHER PINEAL TUMORS

- **PAPILLARY TUMOR OF THE PINEAL REGION**
    - Densely cellular with **combination of papillary and solid architecture** and **ependymoma-like** features
    - **Uniformly round nuclei with stippled chromatin**
    - IHC: (+) cytokeratins (esp. **CK8/18**), **S100**, NSE; (+/-) GFAP**;** (-) Kir7.1



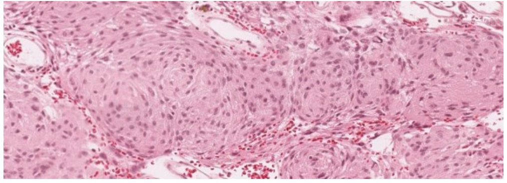
S100 CK8/18 GFAP

IHC images courtesy: Pepe Jiménez Heffernan, MD

- **DESMOPLASTIC MYXOID TUMOR OF THE PINEAL REGION, SMARB1-MUTANT**
    - Cords of oval to spindled cells in desmoplastic, densely collagenized background and loose myxoid matrix
    - IHC: **loss of nuclear SMARCB1** (INI1); (+) CD34, EM

MENINGIOMA

Meningothelial whorls

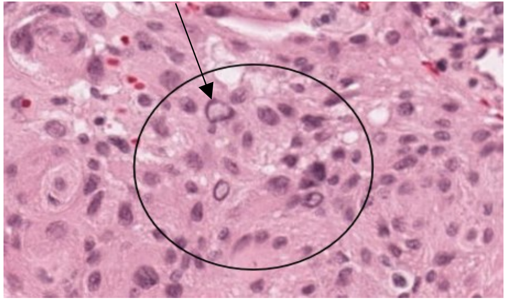


MENINGIOMA

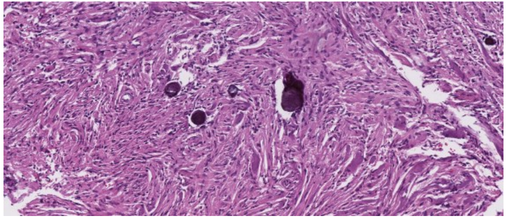
MORPHOLOGY

- Oval nuclei with delicate chromatin
- Frequent nuclear **pseudoinclusions**
- **Syncytial** tumor cells with abundant eosinophilic cytoplasm
- **Whorls and psammoma** bodies are common

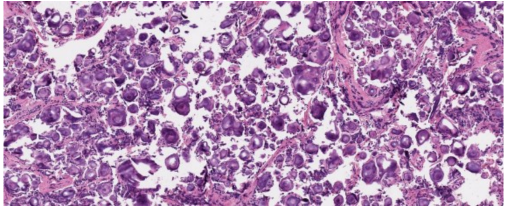
Nuclear pseudoinclusions



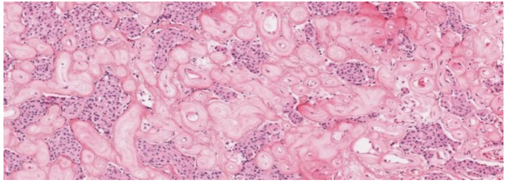
Fibrous meningioma with psammoma bodies



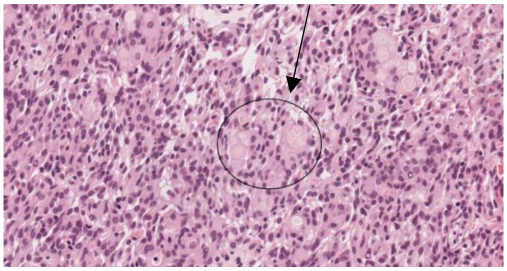
Psammomatous meningioma



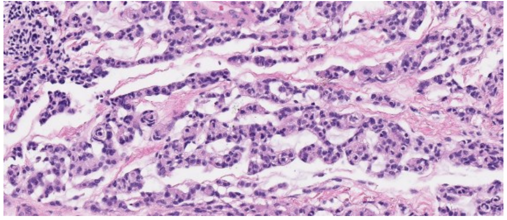
Angiomatous meningioma



Secretory meningioma with pseudopsammoma bodies



Chordoid meningioma

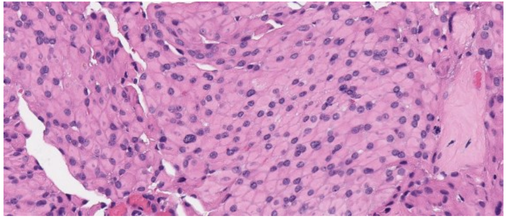


- Numerous histologic patterns:
  - **Meningothelial** – classic morphology with **whorls** of syncytial epithelioid cells
  - **Fibrous** – spindled cells with abundant background collagen
  - **Transitional (mixed)** – combination of meningothelial and fibrous histologies (most common)
  - **Psammomatous** – numerous psammoma bodies; often seen in the thoracic spine of middle-aged to elderly women
  - **Angiomatous** – predominance of blood vessels (often hyalinized), associated with peritumoral edema
  - **Microcystic** – cells with thin elongated processes in a cobweb-like background
  - **Secretory** – gland-like spaces containing PAS-positive eosinophilic material ("pseudopsammoma bodies")
  - **Lymphoplasmacytic-rich** – extensive chronic inflammatory infiltrates (plasma cells may be scant)
  - **Metaplastic** – presence of mesenchymal components, including osseous, cartilaginous, lipomatous, myxoid, and xanthomatous elements
  - **Chordoid** – eosinophilic and vacuolated cells arranged in chords/trabeculae in a mucoid matrix (mimics chordoma); higher risk of recurrence (CNS WHO Grade 2)
  - **Clear cell** – sheets of polygonal cells with clear, glycogen-rich cytoplasm and prominent perivascular and interstitial collagen; SMARCE1 mutations common; higher risk of recurrence (CNS WHO Grade 2)
  - **Papillary** – perivascular pseudopapillary architecture; cells often discohesive, giving the appearance of pseudorosettes; PBRM1 > BAP1 mutations; aggressive behavior (CNS WHO Grade 3)
  - **Rhabdoid** – rhabdoid cells with abundant eosinophilic cytoplasm, eccentrically placed nuclei, and prominent nucleoli; BAP1 > PBRM1 mutations; aggressive behavior (CNS WHO Grade 3)
- **Atypical meningioma** has higher **mitotic rate**, presence of atypical histologic features, and/or brain invasion (see grading below)
- **Anaplastic** (malignant) meningioma has a **markedly elevated mitotic rate** and often loses the classic histologic features of meningioma; can demonstrate carcinoma-like, melanoma-like, or sarcoma-like histologic features

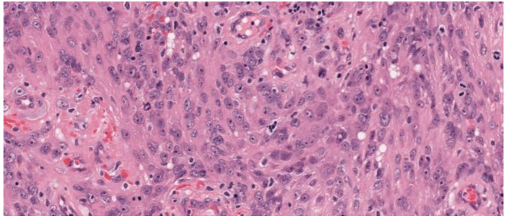
OTHER HIGH YIELD POINTS

- **Most common intracranial tumor**
- Tumor of the **dura mater** – lateral convexities most common but can occur anywhere in the intracranial, intraspinal, or orbital compartments; rarely forms in the lateral ventricles
- Usually **slow-growing and benign**
- More common in adults, F>M
- Characteristic **"dural tail"** sign on neuroimaging
- IHC: **(+) SSTR2A, EMA, PR**
- Monosomy 22 and NF2 gene alterations are common
- Grading criteria should be applied regardless of the underlying histologic subtype
  - The presence of focal clear cell/chordoid/papillary/rhabdoid features without other high-grade features does not warrant classification to higher WHO grade

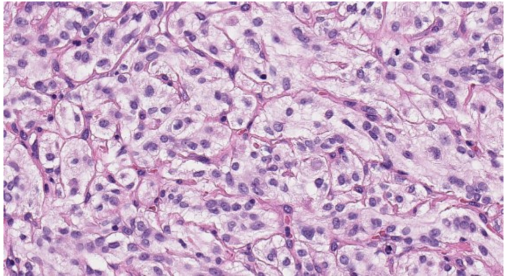
Rhabdoid meningioma



Anaplastic meningioma, prominent nucleoli



Clear cell meningioma



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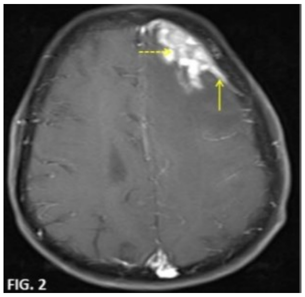
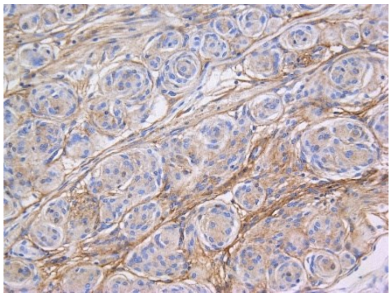
GRADING OF MENINGIOMA	
Grade 1	<4 mitoses per 10 high power fields AND <3 atypical features (see below)
Grade 2	4-19 mitoses per 10 high power fields OR Brain invasion OR Chordoid or clear cell histology OR At least 3 of 5 atypical features: 1. High tumor cellularity 2. High N:C ratio (small cell change) 3. Prominent nucleoli 4. Sheeting architecture 5. Tumor necrosis
Grade 3	≥20 mitoses per 10 high power fields OR Anaplastic histology (melanoma-, carcinoma-, or sarcoma-like histology) OR Papillary or rhabdoid histology OR TERT promoter mutation OR CDKN2A/B homozygous deletion



Dural tail sign



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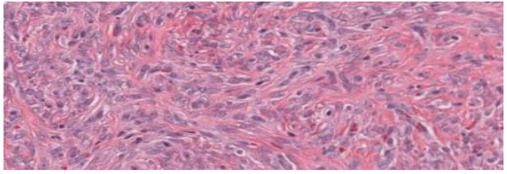
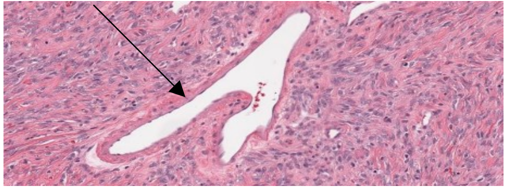
UNIQUE MESENCHYMAL TUMORS

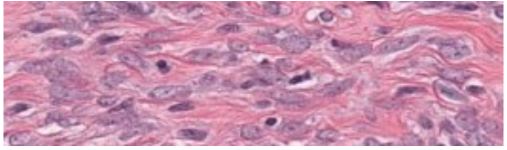
Patternless pattern of spindled cells



Staghorn vessel



Collagenous background



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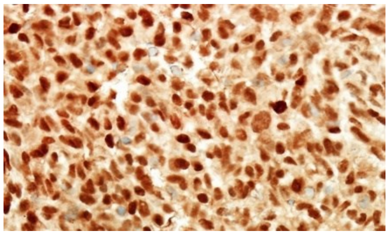
SOLITARY FIBROUS TUMOR (CNS WHO Grade 1-3)

MORPHOLOGY

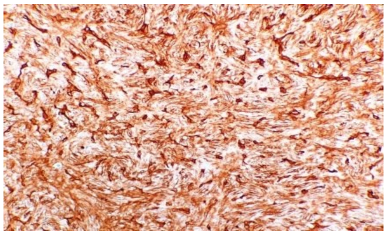
- **Fibroblastic tumor** with histologic spectrum, variable cellularity
- "**Patternless pattern**" of bland spindled to ovoid tumor cells with scant cytoplasm in a **collagenous** (sometimes keloidal) background
- Thin walled, branching blood vessels ("**Staghorn**")

OTHER HIGH YIELD POINTS

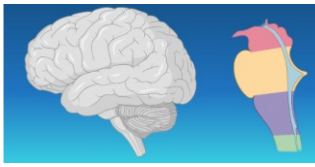
- Usually **dural based** in adult patients
- IHC: **(+) STAT6, CD34**
- Molecular hallmark: **NAB2-STAT6 fusion** (paracentric inversion of chr 12q13)
- Grading based on mitotic activity and necrosis:
  - ➢ Grade 1: <5 mitoses / 10 HPF
  - ➢ Grade 2: ≥5 mitoses / 10 HPF without necrosis
  - ➢ Grade 3: ≥5 mitoses / 10 HPF with necrosis

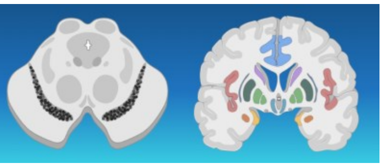


STAT 6

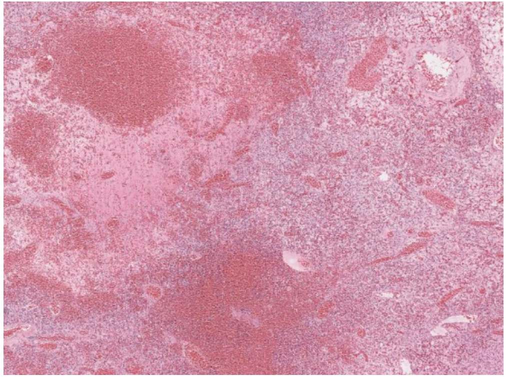


CD34

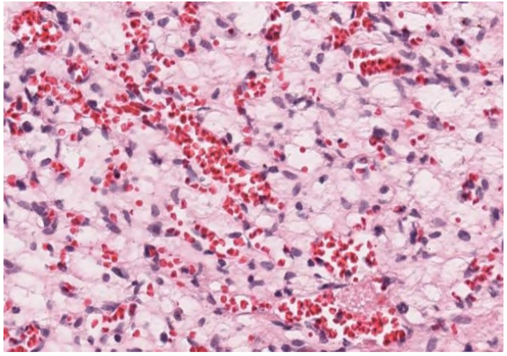




Richly vascular with intervening stromal cells



Large stromal cells with vacuolated cytoplasm



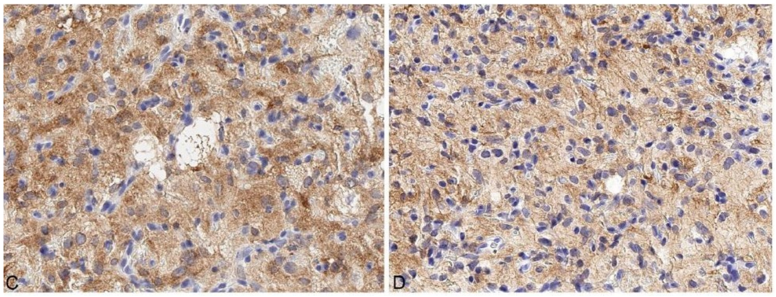
HEMANGIOBLASTOMA (CNS WHO Grade 1)

MORPHOLOGY

- Two characteristic components:
  - **Large stromal cells** with **vacuolated to clear cytoplasm**
  - Abundant **vasculature**
- Can be histologically **identical** to metastatic **clear cell renal cell carcinoma**

OTHER HIGH YIELD POINTS

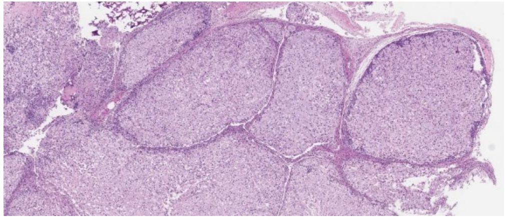
- Located in the **cerebellum** of adult patients
- Associated with **von Hippel-Lindau (VHL) disease**; important to differentiate from metastatic ccRCC
- IHC: **(+) inhibin, NSE,** brachyury; (-) PAX8, CAM5.2, CD10, EMA
- Molecular: **VHL** gene alterations (chromosome 3p25)



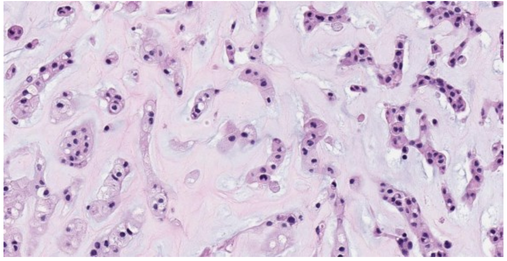
Inhibin NSE

Path Presenter IHC image courtesy: Darcy A. Kerr @darcykerrMD

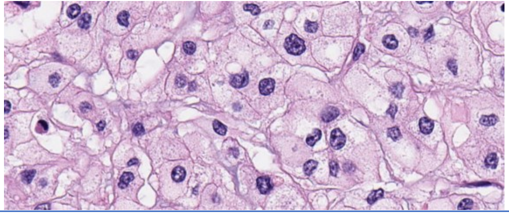
Lobular architecture with fibrous septa



Cords of tumor cells in myxoid background



Physaliphorous cells



CHORDOMA

MORPHOLOGY

- **Cords or ribbons** of neoplastic cells in a **myxoid** background
- Large tumor cells with vacuolated, bubbly cytoplasm (“**physaliphorous** cells”)
- **Lobular** architecture divided by fibrous septa
- May contain an extracellular matrix resembling **hyaline cartilage** (chondroid chordoma)
- **Dedifferentiated** chordoma contains two histologic elements:
  - Conventional chordoma
  - Juxtaposed high-grade **sarcoma**
- **Poorly differentiated** chordoma composed of dense sheets of **epithelioid and rhabdoid cells and lacks physaliphorous cells**

OTHER HIGH YIELD POINTS

- Primary malignant bone neoplasm derived from notochord elements
- Always located along the axial skeleton, most commonly along the **sacrococcygeal region or skull base** (clivus)
- Usually, adults, poorly differentiated chordoma tends to occur in children
- IHC: **(+) brachyury**, pancytokeratin, EMA, S100
  - Dedifferentiated chordoma tends to lose expression of these markers
  - **Poorly differentiated** chordoma shows **loss of SMARCB1 (INI1)** expression

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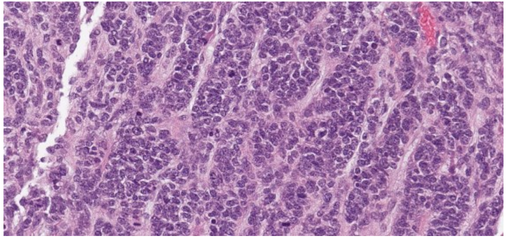
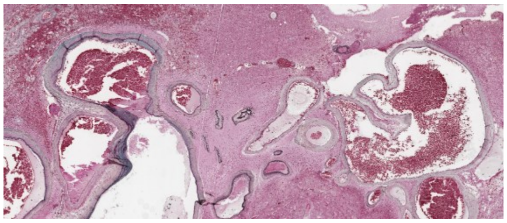
CIC-rearranged sarcoma



Arteriovenous malformation



OTHER CNS MESENCHYMAL TUMORS

- Intracranial mesenchymal tumor, FET-CREB fusion-positive
- CIC-rearranged sarcoma: IHC: (+) NUT
- Primary intracranial sarcoma, DICER1-mutant: PAS (+) eosinophilic cytoplasmic granules
- Ewing sarcoma
- Rhabdomyosarcoma
- Mesenchymal chondrosarcoma, conventional chondrosarcoma
- Hemangioma
- Vascular malformations:
  - Arteriovenous malformation (AVM): variably dilated, thick-walled blood vessels with intervening brain tissue
  - Cavernous malformation: dilated, back-to-back, thin-walled blood vessels without intervening brain tissue

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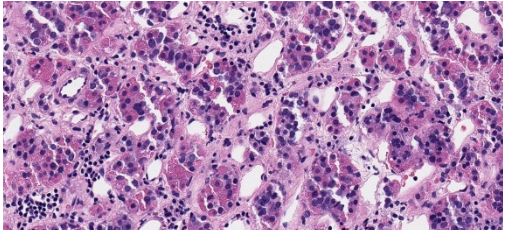
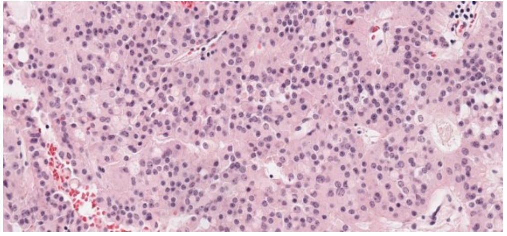
SELLA REGION TUMORS

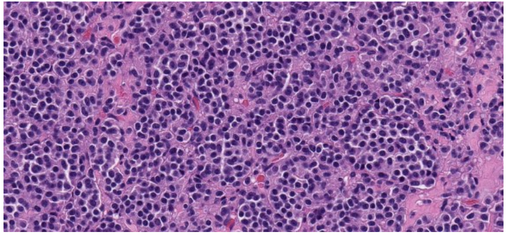
Normal pituitary: mixture of cells, small acini



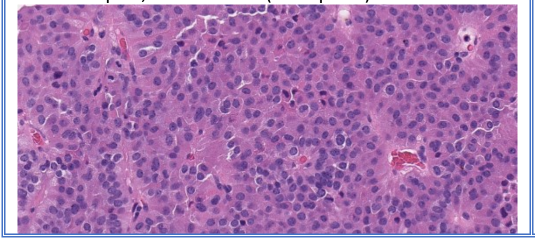
Diffuse growth (chromophobic)



Expanded acinar architecture (basophilic)



Monomorphic, round nuclei (acidophilic)



PITUITARY ADENOMA / PITUITARY NEUROENDOCRINE TUMOR

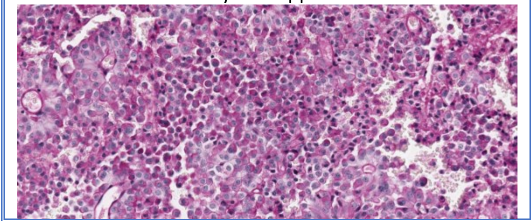
MORPHOLOGY

- Neoplasm of hormone-producing anterior pituitary cells
- **Monomorphic** neuroendocrine cells, round nuclei, speckled chromatin
- Cells can be **acidophilic, basophilic, or chromophobic** (nonspecific)
- Variety of histologic patterns: **diffuse, papillary, trabecular**
- **Touch prep:** cellular, discohesive, homogeneous neuroendocrine population
- Reticulin stain highlights **expanded acinar architecture**
- **Crooke cell adenoma**: abundant accumulation of pale hyaline material in cytoplasm; mostly ACTH producing (Cushing's disease), marked concentric staining pattern with cytokeratin
- **Hemorrhagic necrosis** can be seen in large tumors → **pituitary apoplexy**

OTHER HIGH YIELD POINTS

- Most common tumor of the sellar region
- Benign but **can invade** adjacent structures
- IHC: **(+) synaptophysin, chromogranin; (-) S100**
- Subclassification based on hormone secretion → utilize IHC panel
- Three lineages, based on transcription factor expression profile: TPIT, PIT1, and SF1
- Functioning adenomas secrete hormones and cause symptoms related to hormone secretion
  - **Lactotroph** (PIT1-lineage): most common (~50% of adenoma); prolactin → galactorrhea & amenorrhea (women) or sexual dysfunction (men)
  - **Corticotroph** (TPIT-lineage): ACTH → excessive cortisol → Cushing's disease
  - **Gonadotroph** (SF1-lineage): FSH, LH, and/or alpha-subunit → menstrual disturbances in women or sexual dysfunction in men
  - **Somatotroph** (PIT1-lineage): GH → gigantism/acromegaly
  - **Thyrotroph** (PIT1-lineage): (rare) TSH → hyperthyroidism
  - **Null cell** (lacks distinct lineage): does not produce hormones
  - **Plurihormonal**: multiple hormones
- Silent adenomas are IHC(+) but do not secrete hormone
- Non-functioning adenomas do not secrete hormones; symptoms related to **mass effect** (bitemporal hemianopsia, diplopia, headache)

Crooke cell adenoma: hyaline appearance



- **Pituitary carcinoma** (very rare) defined by craniospinal dissemination and/or systemic metastasis, **predictive markers of malignant progression not well established**

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PITUITARY BLASTOMA

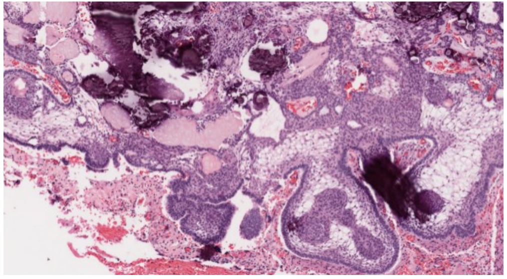
MORPHOLOGY

- Embryonal neoplasm of sellar region
- Three components:
  - Primitive **blastemal** cells – small, chromophobic, and undifferentiated
  - **Neuroendocrine** cells – round nuclei and abundant cytoplasm arranged in lobules or sheets
  - **Rathke pouch epithelium** – cuboidal to columnar cells forming gland-like structures

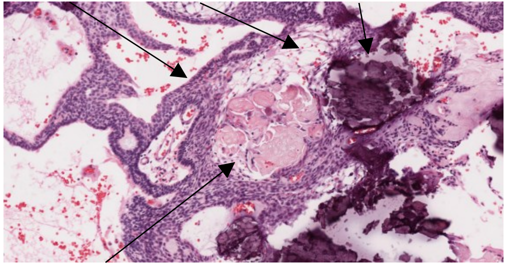
OTHER HIGH YIELD POINTS

- **Extremely rare**, occurs in **infants**
- Commonly present with **Cushing syndrome** due to elevated ACTH
- Associated with germline and somatic **DICER1 mutations**
- IHC: **(+) ACTH; high Ki67**

Mixed squamous epithelial tumor



Basal layer, stellate reticulum, calcifications



“Wet” keratin

ADAMANTINOMATOUS CRANIOPHARYNGIOMA (CNS WHO Grade 1)

MORPHOLOGY

- **Mixed solid and cystic squamous epithelial tumor**
- Basal layer with **basal palisading**
- **Stellate reticulum** (loose background)
- “Wet” keratin, calcifications, cholesterol clefts, xanthogranulomatous reaction
- Gross: “**machine oil**” cyst fluid

OTHER HIGH YIELD POINTS

- **Bimodal** age distribution (1st and 5th decades)
- Adamantinomatous variant represent almost all craniopharyngiomas in children and ~80% of craniopharyngiomas in adults
- Thought to arise from elements related to Rathke’s pouch
- IHC: **nuclear expression of beta-catenin**; (+) p63
- Molecular: **Activating CTNNB1 mutations** (encodes beta-catenin)
- Malignant progression is extremely rare

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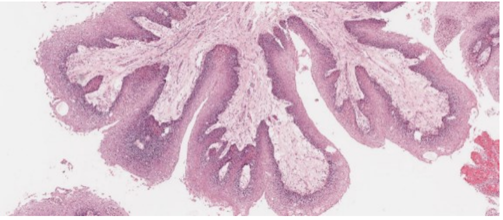
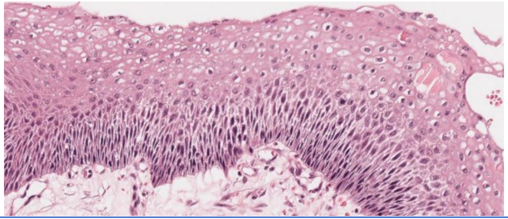
Papillary architecture



Non-keratinizing squamous epithelium



PAPILLARY CRANIOPHARYNGIOMA (CNS WHO Grade 1)

MORPHOLOGY

- **Resembles a squamous papilloma**: non-keratinizing epithelium with fibrovascular cores
- Solid sheets
- Lacks stellate reticulum, “wet” keratin, calcifications
- Well demarcated tumor-brain interface

OTHER HIGH YIELD POINTS

- Exclusively in adults
- IHC: **(+) BRAF V600E mutation antibody, p63**
- Molecular: BRAF V600E mutation
- Malignant progression extremely rare

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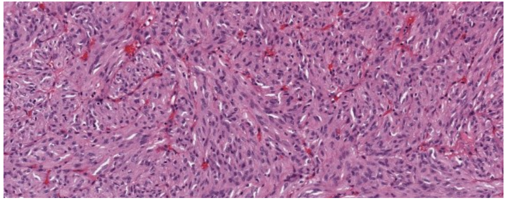
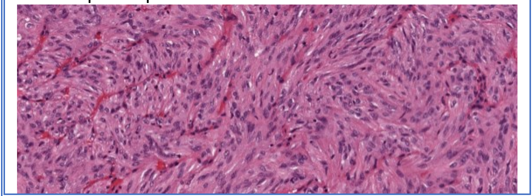
Storiform pattern



Bland bipolar spindle cells



PITUICYTOMA

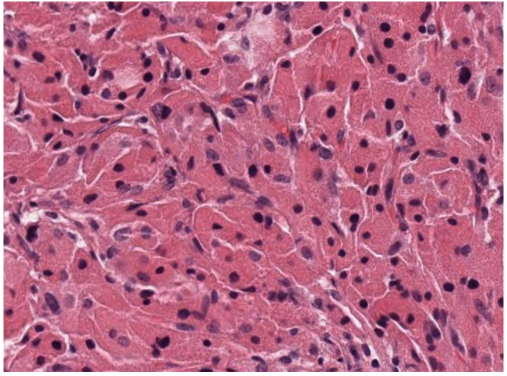
MORPHOLOGY

- Low-grade glial tumor composed of **bland bipolar spindle cells** arranged in a **fascicular or storiform** pattern
- Fibrillary background
- Circumscribed, solid
- Lacks Rosenthal fibers, eosinophilic granular bodies, hyalinized blood vessels

OTHER HIGH YIELD POINTS

- Rare, primarily adults
- Tumor of **posterior pituitary/infundibulum**
- IHC: **(+) TTF1, S100; (+/-) GFAP; (-) synaptophysin**
- Good prognosis
- Likely on a spectrum with granular cell tumor of the sellar region and spindle cell oncocytoma (see below)

Abundant granular eosinophilic cytoplasm



GRANULAR CELL TUMOR OF THE SELLAR REGION

MORPHOLOGY

- Densely packed polygonal cells with abundant **granular eosinophilic cytoplasm** (lysosomes – PAS(+), diastase resistant)
- **Perivascular lymphocytes**

OTHER HIGH YIELD POINTS

- Rare, primarily adults
- Tumor of **posterior pituitary/infundibulum**
- IHC: **(+) TTF1, CD68; (+/-) S100**
- Slow progression and benign clinical course

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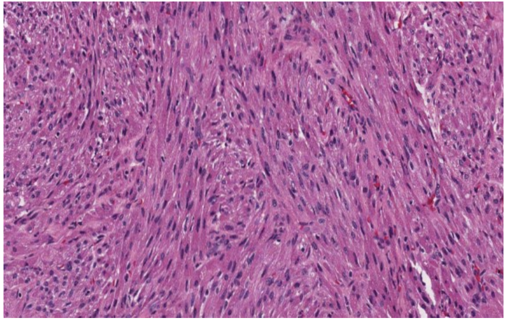
Spindled cells in intersecting fascicles



SPINDLE CELL ONCOCYTOMA

MORPHOLOGY

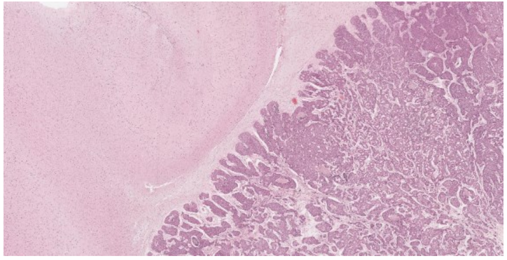
- **Spindled to epithelioid oncocytic** non-neuroendocrine neoplasm of the posterior pituitary
- **Intersecting fascicles** and poorly defined nodules
- **Variable nuclear pleomorphism**

OTHER HIGH YIELD POINTS

- Rare, primarily adults
- IHC: **(+) TTF1, S100, EMA**
- Good prognosis but higher rate of recurrence than pituicytoma and granular cell tumor of the sellar region

CNS METASTASES

Clear demarcation from adjacent brain

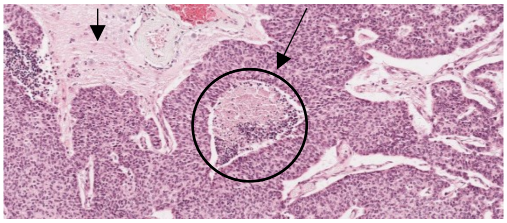


METASTATIC CNS LESIONS

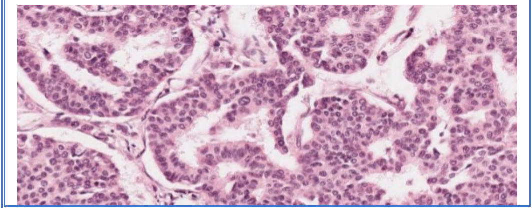
MORPHOLOGY

- Histomorphology and immunophenotype generally resembles that of primary tumor
- Well-circumscribed and **clearly demarcated** from adjacent brain
- Occasionally, metastatic small cell neoplasms, lymphoma, and melanoma can show an infiltrative growth pattern
- **Tumor necrosis** can be extensive

Reactive brain tissue and tumor necrosis



Metastatic adenocarcinoma



OTHER HIGH YIELD POINTS

- **Most common CNS malignancy in adults**
- Most common site of origin:
  - Men: 1) lung, 2) gastrointestinal, 3) melanoma, 4) kidney
  - Women: 1) lung, 2) breast, 3) gastrointestinal, 4) melanoma
  - Children: 1) leukemia/lymphoma, 2) germ cell tumors, 3) osteosarcoma, 4) neuroblastoma
- Usually multiple, well-circumscribed lesions
- Majority (80%) in cerebral hemispheres, particularly at the arterial border zones and gray-white junction
- Metastases can also occur to the dura, leptomeninges, and sellar region

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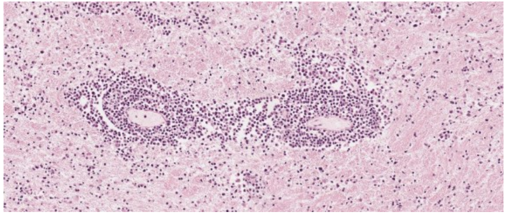
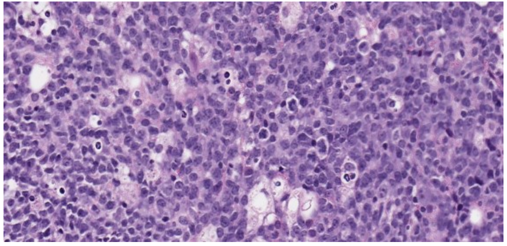
MISCELLANEOUS

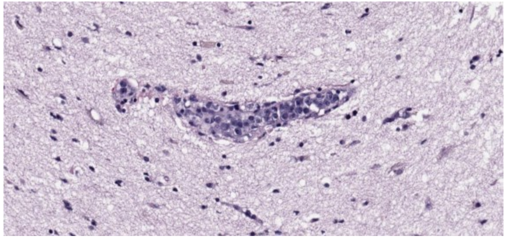
Vasculocentric distribution of CNS lymphoma



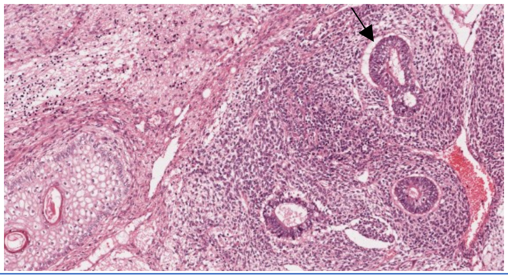
Diffuse large B-cell lymphoma of the CNS (PCNSL)



Intravascular lymphoma



Immature teratoma with rosette formation



HEMATOLYMPHOID NEOPLASMS

PRIMARY DIAGNOSTIC ENTITIES

- Primary CNS lymphoma (PCNSL) – diffuse large B-cell lymphoma
- Immunodeficiency-associated CNS lymphomas
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- MALT lymphoma of the dura
- Anaplastic large cell lymphoma (ALK+/ALK-)
- T-cell and NK/T-cell lymphomas
- Erdheim-Chester disease
- Rosai-Dorfman disease
- Juvenile xanthogranuloma
- Langerhans cell histiocytosis
- Histiocytic sarcoma

OTHER HIGH YIELD POINTS

- The **majority** of CNS lymphomas are **diffuse large B cell lymphoma**
- EBV-associated lymphomas usually in immunocompromised patients
- The majority of **dural** lymphomas are **marginal zone lymphoma**

GERM CELL TUMORS

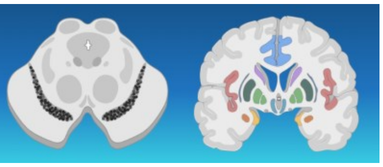
PRIMARY DIAGNOSTIC ENTITIES

- Mature teratoma, immature teratoma, teratoma with somatic-type malignancy
- Germinoma
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma
- Mixed germ cell tumor

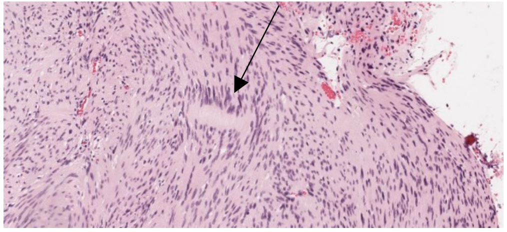
OTHER HIGH YIELD POINTS

- Morphologically and immunophenotypically similar to gonadal and extraneuraxial tumors
- Majority located along **the midline (pineal region** most common) **in children**
- **Pure germinoma is most common**
- Best outcome with mature teratoma (surgically curable) and pure germinoma (highly radiosensitive)

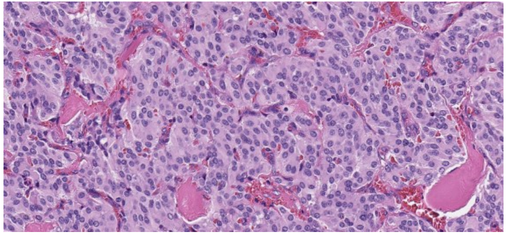
11. NEUROPATHOLOGY



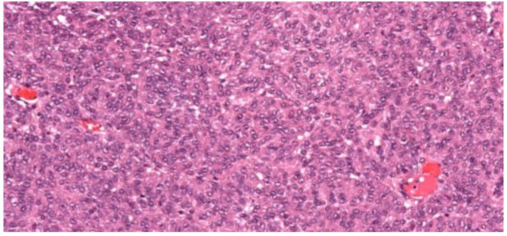
Schwannoma with Verocay body



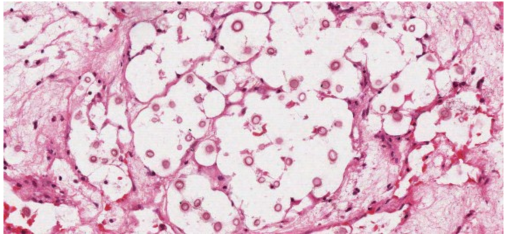
“Zellballen” nests of paraganglioma



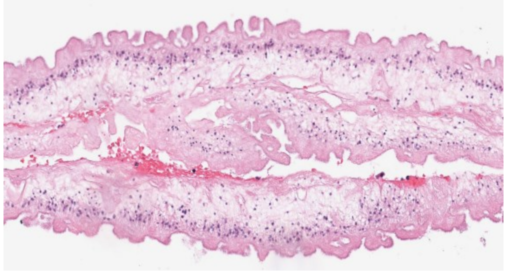
Well-differentiated cells of melanocytoma



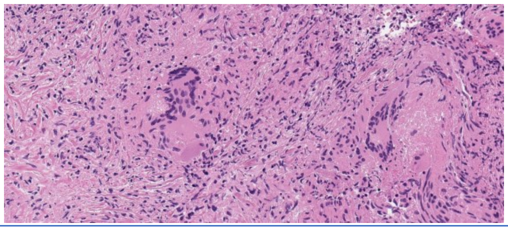
Cryptococcosis



Neurocysticercosis



Granulomas in neurosarcoidosis



NERVE TUMORS

PRIMARY DIAGNOSTIC ENTITIES

- Schwannoma
- Neurofibroma
- Perineurioma
- Hybrid nerve sheath tumors
- Malignant melanotic nerve sheath tumor
- Malignant peripheral nerve sheath tumor
- Cauda equina neuroendocrine tumor (previously paraganglioma)

OTHER HIGH YIELD POINTS

- Mostly sporadic but also associated with tumor predisposition syndromes: NF1, NF2, schwannomatosis, and Carney complex
- Malignant melanotic peripheral nerve sheath tumor (formerly melanotic schwannoma) is now thought to be a distinct entity

PRIMARY MELANOCYTIC TUMORS

PRIMARY DIAGNOSTIC ENTITIES

- Melanocytosis & melanomatosis (diffuse meningeal neoplasms)
- Melanocytoma & melanoma (circumscribed meningeal neoplasms)

OTHER HIGH YIELD POINTS

- Arise from melanocytes normally found in the leptomeninges
- Range from **well-differentiated tumors to frankly malignant**
- Share molecular features of **ocular** melanoma (**GNAQ and GNA11** mutations most common) rather than epidermal melanoma

CNS INFECTIONS

PRIMARY DIAGNOSTIC ENTITIES

- Subdural and cerebral bacterial abscesses
- Syphilitic gumma
- Tuberculoma
- Fungal infections (Candidiasis, Aspergillosis, Cryptococcosis)
- Protozoal infections (Toxoplasmosis, cerebral malaria, amebiasis)
    - Neurocysticercosis: cysts with three layers: cuticular, cellular, reticular
- Viral infections (HSV, CMV, Enterovirus, Arbovirus, HIV, rabies)
    - Progressive multifocal leukoencephalopathy (PML): JC virus
- Prion disease: infectious proteins, Creutzfeldt-Jakob disease, spongiform degeneration

INFLAMMATORY AND DEMYELINATING CONDITIONS

PRIMARY DIAGNOSTIC ENTITIES

- Tumefactive multiple sclerosis
- CNS vasculitis
- Neurosarcoidosis
- Autoimmune encephalitis
- Rasmussen encephalitis

OTHER HIGH YIELD POINTS

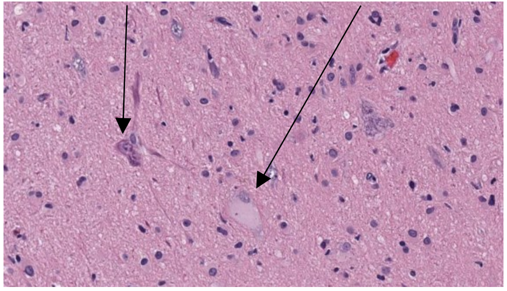
- Diagnostic yield for CNS vasculitis is highest when sampling from dura, leptomeninges, and cortical parenchyma

EPILEPSY-RELATED SURGICAL NEUROPATHOLOGY

PRIMARY DIAGNOSTIC ENTITIES

- Focal cortical **dysplasia**

Dysmorphic neurons in cortical tuber, balloon cell



- **Cortical tubers (tuberous sclerosis)**
  - Dysmorphic neurons, balloon cells, microcalcifications
- Hippocampal sclerosis

OTHER HIGH YIELD POINTS

- Most patients with intractable epilepsy

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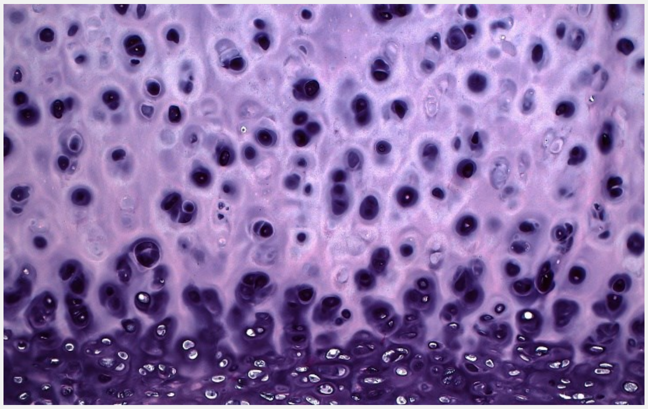
TUMOR SYNDROMES

Syndrome	Gene	Nervous System Tumor(s)	Other manifestations
Neurofibromatosis Type 1 (NF1)	NF1 (AD)	Optic tract pilocytic astrocytomas, astrocytomas, neurofibromas, MPNST	Café-au-lait spots, axillary freckles, osseous lesions, Lisch nodules, GIST etc.
Neurofibromatosis Type 2 (NF2)	NF2 (AD)	Bilateral vestibular schwannomas (and elsewhere), meningiomas, gliomas, and developmental lesions	Ocular abnormalities
Schwannomatosis	SMARCB1 or LZTR1 (Sporadic)	Multiple schwannomas and meningiomas	Rare
Von Hippel Lindau Disease (VHL)	VHL (AD)	Hemangioblastoma	Clear cell renal cell carcinoma, pheochromocytoma, pancreas NET, ear and epididymis tumors
Tuberous sclerosis	TSC1 or TSC2 (AD)	SEGA, cortical hamartomas, subependymal glial nodules	Cutaneous angiofibroma, cardiac rhabdomyomas, renal angiomyolipoma, lung LAM
Li-Fraumeni Syndrome	TP53 (AD)	Astrocytoma, glioblastoma, medulloblastoma, choroid plexus carcinoma	Multiple primary tumors in children and young adults including: breast cancer, soft tissue sarcomas, adrenal cortical carcinoma, and osteosarcoma
Cowden Syndrome	PTEN (AD)	Dysplastic cerebellar gangliocytoma (Lhermitee-Duclos disease)	Breast, endometrium, and thyroid cancer; multiple hamartomas including skin and GI
Turcot Syndrome	APC (AD)	Medulloblastoma	Colon Cancer, osteomas, fibromatosis
	MMR enzymes(AD)	Gliomas	Café-au-lait macules, lymphoma
Nevoid Basal Cell Carcinoma (Gorlin) Syndrome	PTCH1 or PTCH2 (AD)	Medulloblastoma (desmoplastic/nodular)	Skin basal cell carcinoma, odontogenic keratocytes
Rhabdoid Tumor Predisposition Syndrome	SMARCB1 or SMARCA4	AT/RT	Kidney malignant rhabdoid tumor



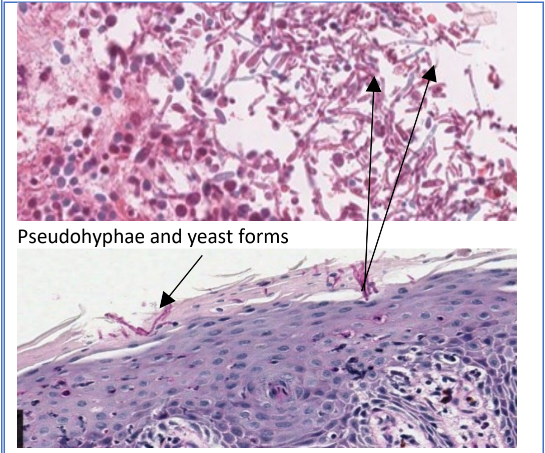
Normal hyaline cartilage from the wall of a trachea.
Courtesy: Ziad El-Zaatari, MD

CHAPTER 12: HEAD AND NECK PATHOLOGY

Terrance Lynn, MD
Maricel Reyes, MD
Vishwajeeth Pasham, MD
Kene Ojukwu, MD
Snehal Sonawane, MD
Jian Li, MD

12. HEAD AND NECK PATHOLOGY

UPPER AERODIGESTIVE TRACT SQUAMOUS LESIONS



Pseudohyphae and yeast forms

CANDIDIASIS

MORPHOLOGY

- Dimorphic fungi (yeast forms and hyphae/pseudohyphae)
- **Hyphal form** causes **tissue invasion/symptoms**
- Often seen with **parakeratosis** and **acute inflammation**
- Can **highlight with PAS or GMS**
- May see accompanying reactive epithelial changes (hyperplasia)

OTHER HIGH YIELD POINTS

- Most common oral fungal infection, endoscopic exam = **white plaque**.
- Often in **immunocompromised** patients, but can occur in healthy
- Immunocompromised: Diabetes, chronic steroid or immune modulator use, immune dysfunction, chronic infection (HIV)

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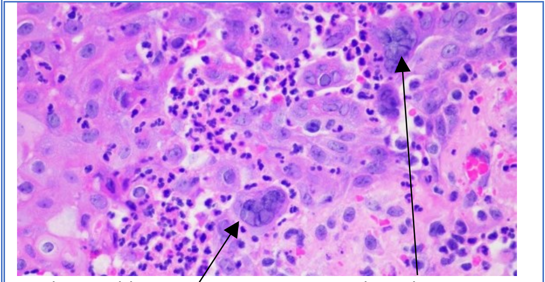

Nuclear molding
Marginated chromatin
Multinucleation

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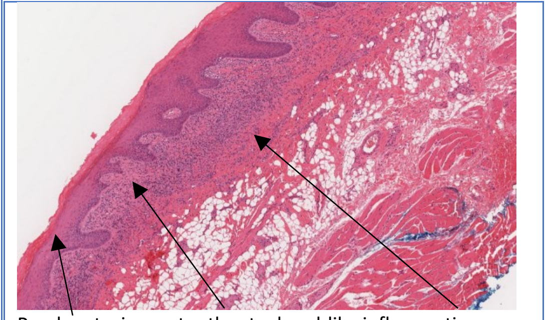
HERPES SIMPLEX VIRUS

MORPHOLOGY

- Infected cells show classic **ground glass intranuclear inclusions**
- Infected cells have the "**3 M's**" (**Molding**, **Margination**, **Multinucleation**)
- Usually, **mucosal ulceration** and **necrosis**
- **Infected cells** can be **seen easily at edges** of ulcer

OTHER HIGH YIELD POINTS

- Virus **infects epithelial cells** and **ganglion cells**
- Lesions **regress** and can **re-appear** during periods of stress
- Two types affect different sites (usually, but can infect both)
  - **HSV 1 = Oral** lesions, **HSV 2 = Genital** lesions
- HSVI/II immunohistochemistry will be **positive** in the nuclei



Parakeratosis, sawtooth rete, band-like inflammation

LICHEN PLANUS

MORPHOLOGY

- Epidermis displays **"Saw-tooth" rete** ridges
- **"Band-like" T-cell infiltrate** in papillary dermis
- **No significant atypia** (otherwise consider dysplasia)
- Variable thickness of epidermis and keratinization

OTHER HIGH YIELD POINTS

- **Chronic, self-limited multifocal inflammatory reaction**
- Associated with many medications and hepatitis C infection
- Clinical picture "5 P's": **P**urple, **P**ruritic, **P**olygonal, **P**lanar, **P**apules

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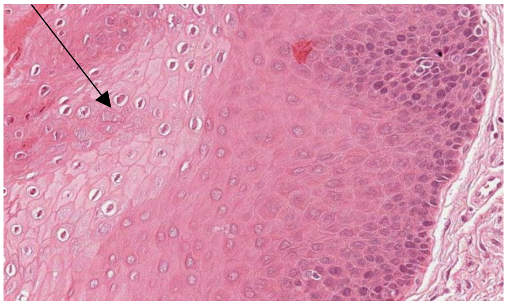
Balloon cells
Acanthosis



HAIRY LEUKOPLAKIA

MORPHOLOGY

- **Acanthosis** and **parakeratosis**
- **"Balloon" cells** in spinous layer (Ballooning degeneration)
- Viral cytopathic effect, including **eosinophilic nuclear inclusions**
- Little to no inflammation and no dysplasia

OTHER HIGH YIELD POINTS

- Causative agent is Epstein-Barr virus (EBV)
- **EBER ISH positive**
- Often occurs on **lateral tongue**
- Most common in **immunocompromised patients**

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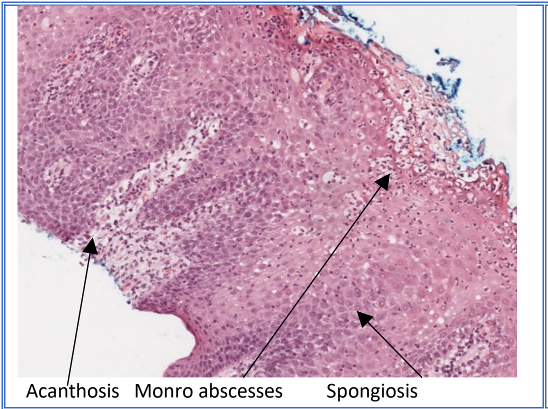
12. HEAD AND NECK PATHOLOGY



GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS)

MORPHOLOGY

- Epithelium with **hyperparakeratosis**, **acanthosis**, **spongiosis**, and collections of neutrophils (**Monro abscesses**)
- Lamina propria has acute and chronic inflammation

OTHER HIGH YIELD POINTS

- **Idiopathic** inflammatory lesion on tongue that is **often asymptomatic**
- Female > Male and usually in 2-3 decade
- Clinically: Presents as multiple, well-defined erythematous islands with raised white serpiginous borders that rapidly appear and migrate

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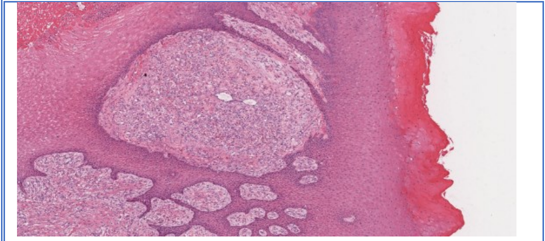
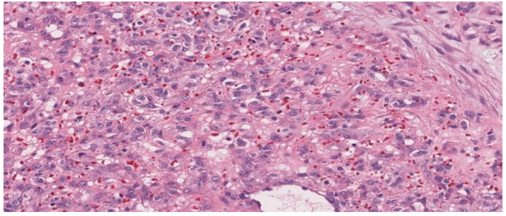


Lobular arrangement of vessels



PYOGENIC GRANULOMA (LOBULAR CAPILLARY HEMANGIOMA)

MORPHOLOGY

- **Mucosal ulceration** with underlying **mixed inflammatory cells**
- Vessels arranged in lobular pattern with dividing fibrous septa
- Vessels often engorged with RBCs
- There is **NO granuloma in pyogenic granuloma** (misnomer)

OTHER HIGH YIELD POINTS

- **Pathogenesis:** biting/trauma and poor oral hygiene
- **Female > Male** and usually in **2-3 decade**
- Most often occur on the gingiva
- Clinically, present as painless ulcerated/bleeding polypoid lesion
- IHC: SMA+, MSA+, CD31+, CD34+, and Factor VIIIR antigen

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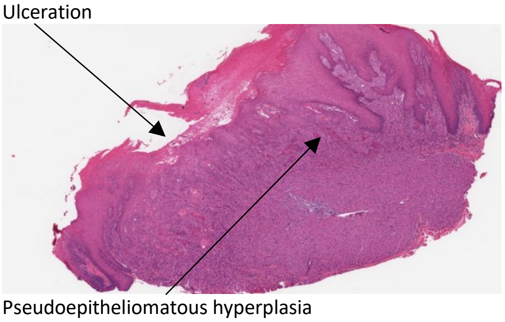
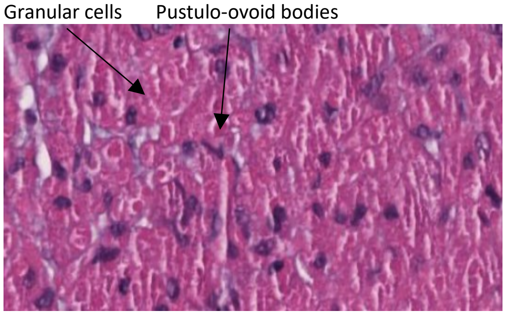




GRANULAR CELL TUMOR

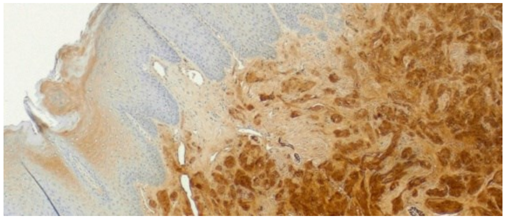
MORPHOLOGY

- Sheets and nests of round to polygonal cells with indistinct borders
- Nuclei are variable (small and dense chromatin to vesicular)
- Eosinophilic cytoplasm with coarse granules (fused/aggregates of **phagolysosomes**), also called pustulo-ovoid bodies of Milian
- Overlying squamous mucosa can show **pseudoepitheliomatous hyperplasia** (if you see this in a superficial sample, look for the granular cells)

OTHER HIGH YIELD POINTS

- Embryologic origin: **Neuroectoderm**
- Slight Female > Male predominance, usually in 3-5 decade
- IHC: **S100+, SOX10+, CD68+**, TFE3+, **CD31-, CD34-, HMB45-,** MSA-
- Molecular mutation: Loss of function in *ATP6AP1* and *ATP6AP2*

IHC: S100



Credit: Xiaoyin " Sara" Jiang MD @Sara_Jiang

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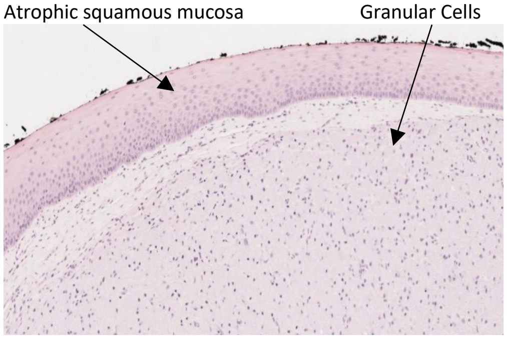
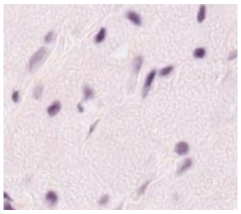
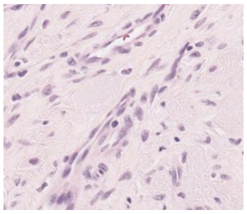
12. HEAD AND NECK PATHOLOGY



Granular cells



Delicate blood vessels



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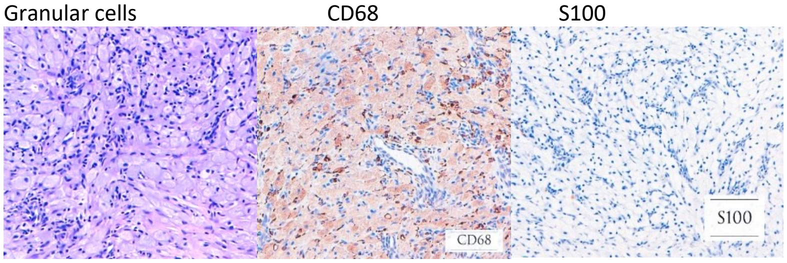
EPULIS (CONGENITAL GRANULAR CELL TUMOR)

MORPHOLOGY

- **Atrophic** squamous mucosa (**no pseudoepitheliomatous hyperplasia**) overlying tumor
- Polygonal cells with small nuclei, **eosinophilic granular cytoplasm**, **indistinct cytoplasmic borders**
- **Delicate** meshwork of **blood vessels**

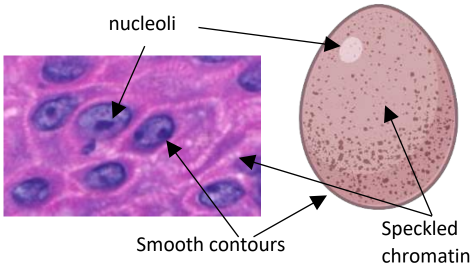
OTHER HIGH YIELD POINTS

- Occurs in **newborns** mostly on alveolar ridge
- **Spontaneous regresses** within first year of life
- It does not recur if incompletely excised
- Predominantly seen in **females**, rare cases in males
- IHC: **Vimentin+, Acid Phosphatase+, S100-** (different than adult)



Credit: Adriana Zucchiatti, MD @zucchiatti_

REACTIVE VERSUS DYSPLASTIC CHANGES



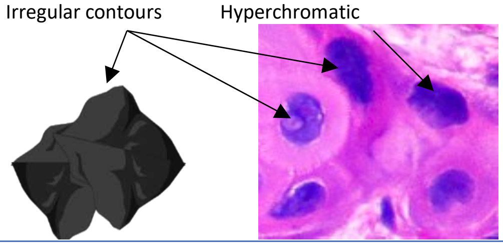
REACTIVE CHANGES

MORPHOLOGY

- Low nuclear to cytoplasm ratio (more cytoplasm than nucleus)
- Round/oval nuclei, smooth nuclear contours, and speckled chromatin

OTHER HIGH YIELD POINTS

- If there are inflammatory cells between the cells or near them, think reactive atypia (set your bar higher to call dysplasia)
- Reactive squamous epithelium will still show maturation in an orderly process



DYSPLASTIC CHANGES

MORPHOLOGY

- High nuclear to cytoplasm ratio (more nucleus than cytoplasm)
- Enlarged hyperchromatic nuclei
- Irregular nuclear borders
- Impaired maturation in low-grade lesions
- Complete absence of maturation in high-grade lesions

NON-HPV MEDIATED SQUAMOUS NEOPLASMS

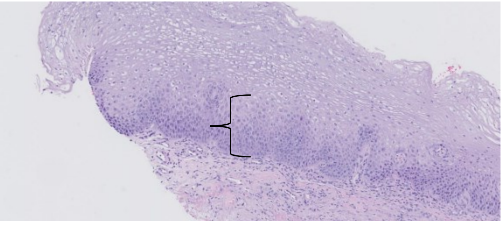
IMPORTANT FACTS

- Most commonly are squamous cell carcinomas
- Arise in the oral cavity, larynx, pharynx

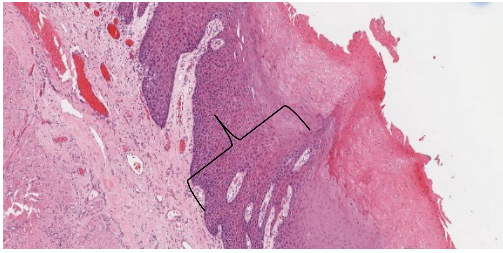
RISK FACTORS

- Most important cause: **Smoking**
- Second most important cause: **Alcohol**
- Other factors: **Chewing tobacco (betel-quid)**
- If using more than one, act synergistic → heightens risk

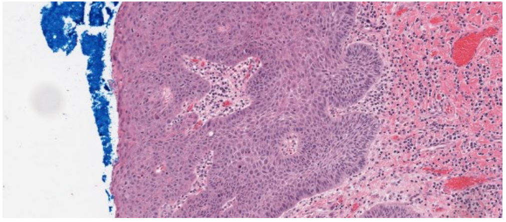
Mild dysplasia (Low-grade)



Moderate dysplasia (High grade)



Severe dysplasia (High grade)



SQUAMOUS DYSPLASIA

Low-grade dysplasia (Mild)	
Architectural Criteria	-Stratification preserved -Retained orientation -Retained maturation pattern
Cytologic Criteria	-At most minimal cellular atypia -Rare mitoses, only in or near basal layer -Few dyskeratotic cells

High-grade dysplasia (Moderate to severe)	
Architectural Criteria	-Abnormal maturation -Altered cells involve ≥1/2 of thickness -Disordered stratification -Can be keratinizing or non-keratinizing -Intact basement membrane -No stromal alterations (desmoplasia)
Cytologic Criteria	-Hyperchromatic nuclei -Irregular nuclear contours -Increased nuclear to cytoplasm ratio -Increased mitoses at or above basal layer -Dyskeratotic or apoptotic cells throughout

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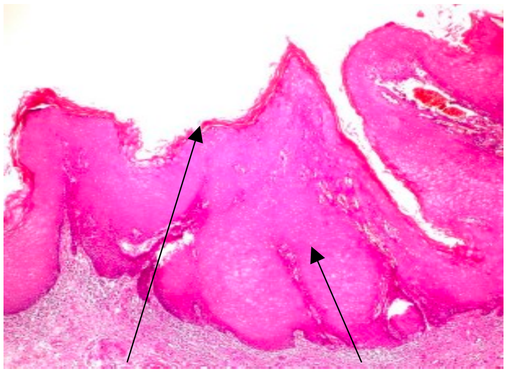
Low Moderate Severe



PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

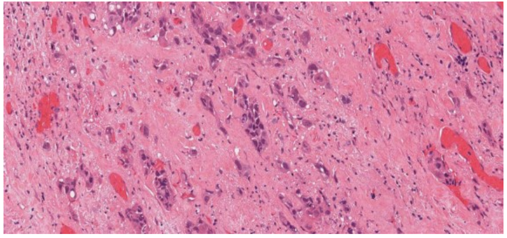
MORPHOLOGY

- Starts as a localized flat hyperorthokeratosis
- As it ages, progresses to verrucous hyperorthokeratosis
- Often has a lichenoid interface mucositis
- Eventually develops dysplasia and can progress to squamous cell carcinoma or verrucous carcinoma
- Entirely exophytic (no downward growth of rete ridges)

OTHER HIGH YIELD POINTS

- Most common locations are in gingiva, alveolar mucosa, and palate
- Mostly seen in older females
- Slow growing and becomes multifocal over time
- No known causative agent

Single cells and tiny infiltrative nests



Skeletal muscle invasion

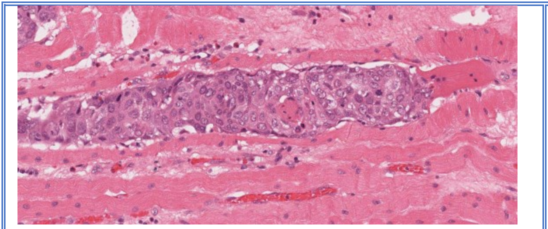
SQUAMOUS CELL CARCINOMA, CONVENTIONAL TYPE

MORPHOLOGY

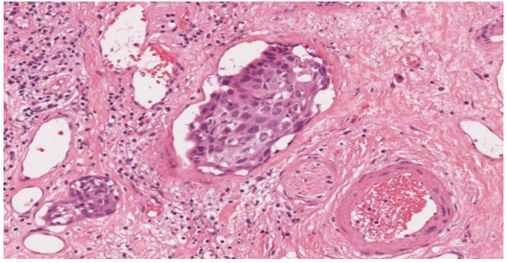
- Malignant epithelial tumor with squamous differentiation
- **Keratinization** (±keratin pearls) and/or **intercellular bridges**
- **Features of invasion**: downward growth of islands, cords, and isolated tumor cells, irregular interface, desmoplastic stromal response, lymphovascular invasion, perineural invasion

OTHER HIGH YIELD POINTS

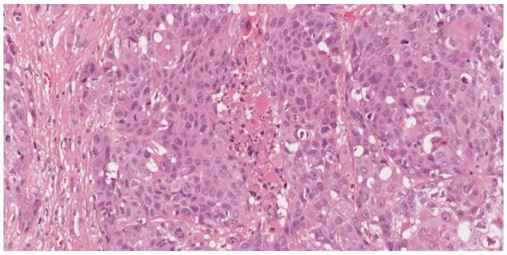
- **Grading** does **NOT** depend on keratinization



Lymphovascular invasion



Necrosis



GRADING SCHEMATA	
Well-differentiated	- Closely resembles normal mucosa - Matures somewhat normally - Has few mitoses
Moderately differentiated	- More pleomorphism - More mitoses
Poorly differentiated	- Basal-type cells predominate with - Numerous conspicuous mitoses - Often lose expression of HMWCKs

- **Symptoms depend on location:** Mass (oral cavity), hoarseness (supraglottic larynx) or dyspnea/stridor (subglottic larynx) etc.
- **Cervical lymph node metastasis** (most adverse prognostic factor)
- **Extracapsular extension** is a particularly associated with **regional recurrence** and **worse survival**
- Male > female (3:1)
- **IHC:** CKAE1/AE3+, CK5/6+, p40+, p63+, CK34 beta E12+, p53+, p16-
- **Negative HPV** DNA/RNA
- **Negative** EBV ISH

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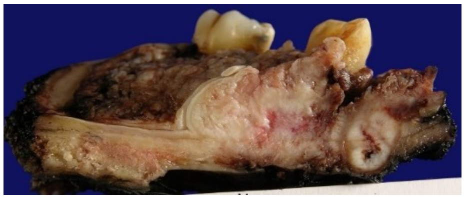
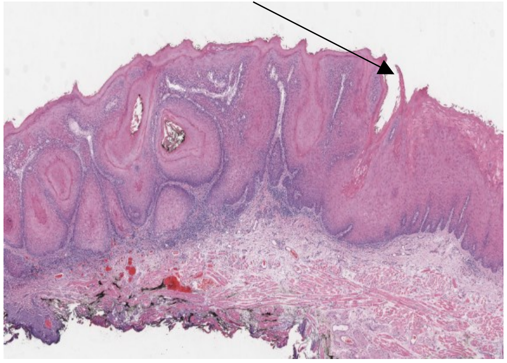
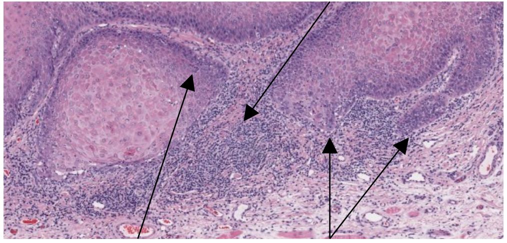


Gross image credit: Cory Nash@iplaywithorgans





VERRUCOUS SQUAMOUS CELL CARCINOMA

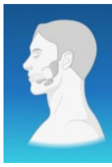
MORPHOLOGY

- **Dramatic acanthosis** with club-shaped projections and invaginations
- Marked "church-spire" keratinization
- **No** significant cytologic atypia
- **NO** infiltrative growth like conventional SCC
- Proliferative basal cell layer only 1-2 cells thick,
- Rare mitosis and are confined to basal layer
- **Well-defined "Pushing" invasion**
- Associated **lymphocytic inflammation** below epithelium

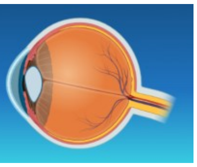
OTHER HIGH YIELD POINTS

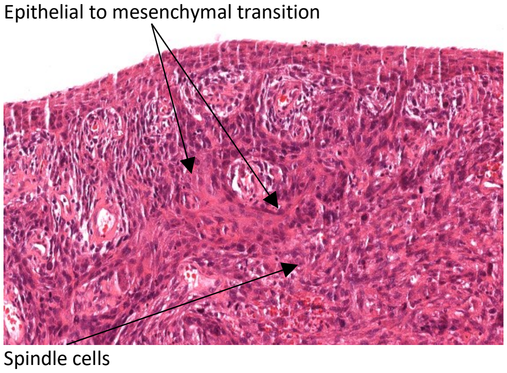
- Variant of well-differentiated squamous cell carcinoma
- Often need to see nearby epithelium to show ***relative* invasion** beneath basal layer of nearby epithelium
- **Locally destructive**/invasive
- **Does not metastasize**
- May be very hard to diagnose on small biopsies
- If clinically concerned for malignancy, but biopsy looks like benign, consider this diagnosis
- If infiltrative growth, then think Conventional SCC

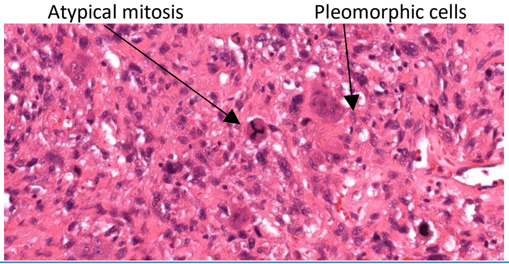
Path Presenter



12. HEAD AND NECK PATHOLOGY







SPINDLE CELL SQUAMOUS CELL CARCINOMA

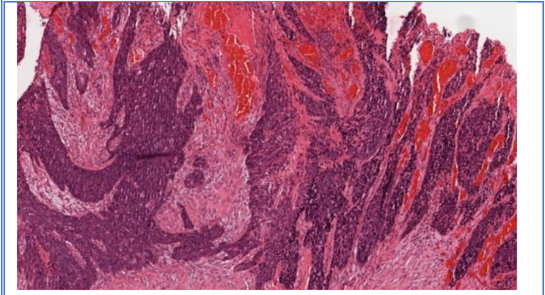
MORPHOLOGY

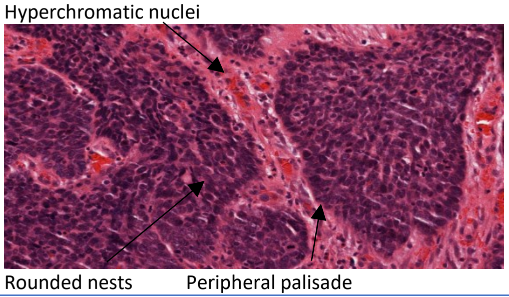
- Squamous cell carcinoma variant with predominantly **malignant spindle and/or pleomorphic cells**
- **Epithelial** to **mesenchymal** transition
- **Often** have atypical mitoses (tripolar or other bizarre forms)

OTHER HIGH YIELD POINTS

- About 70% present with a polypoid mass, rest are ulcerated and sessile
- Often seen in **50 years old, men**
- History of tobacco or alcohol use, and often have poor oral hygiene
- Very **aggressive**, mean survival is <2 years
- **Metastases have variable morphology** (potential pitfall)
- **Difficult diagnosis** if only have spindle cells or metastasis
- **Must have evidence of epithelial differentiation** (morphology or IHC)
- May have to rule out other lesions (sarcoma etc.)
- **IHC:** Usually Keratin+ (about 50%), variable mesenchymal markers (actin, desmin)

Path Presenter





BASALOID SQUAMOUS CELL CARCINOMA

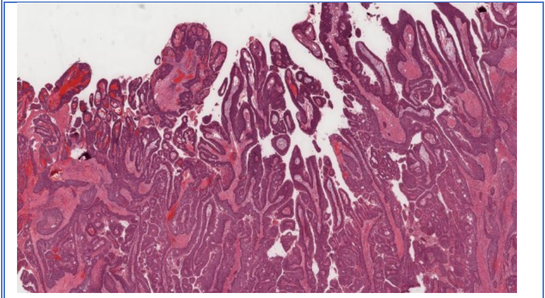
MORPHOLOGY

- **Basaloid** squamous cells in rounded nests with peripheral palisading and admixed hyalinized stroma
- **Hyperchromatic** appearance with high N: C ratio
- Frequent mitoses and **comedonecrosis**

OTHER HIGH YIELD POINTS

- **Uncommon and aggressive**
- Most are metastatic at time of diagnosis
- Nearly all occur in **older** patients with smoking and alcohol use
- Male predominance (9:1)
- **HPV negative** (**NOT** associated with HPV infection)
- May mimic a salivary gland neoplasm
- **IHC:** SOX10+, diffuse p40/p63+, EMA+, Cam5.2+, CK34 beta E12+

Path Presenter



Papillary growth pattern >70% of lesion

PAPILLARY SQUAMOUS CELL CARCINOMA

MORPHOLOGY

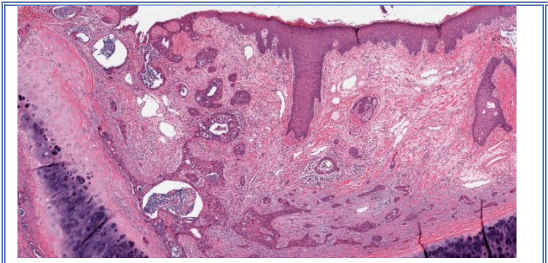
- **Exophytic papillary** growth pattern with thin fibrovascular cores
- **Entirely** covered by **severely** dysplastic basaloid cells
- **At least 70%** of tumor must be papillary

OTHER HIGH YIELD POINTS

- **Uncommon**, questionable association with HPV

Path Presenter

12. HEAD AND NECK PATHOLOGY

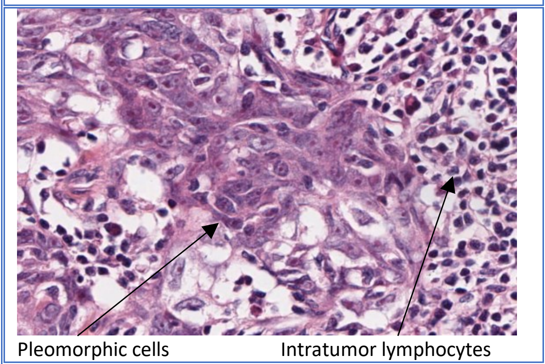


ADENOSQUAMOUS CARCINOMA

MORPHOLOGY

- Malignant squamous cells that exhibit both a squamous and a glandular differentiation
- Can have necrosis in glandular component

Path Presenter


Pleomorphic cells
Intratumor lymphocytes

LYMPHOEPITHELIAL CARCINOMA

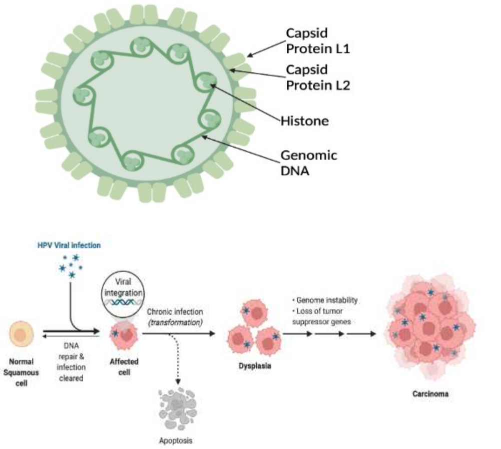
MORPHOLOGY

- **Sheets** and **cords** of **polygonal large syncytial cells** with **eosinophilic cytoplasm** and **vesicular nucleoli**
- Scattered **spindle cells**
- Abundant **lymphoplasmacytic infiltrate**

OTHER HIGH YIELD POINTS

- Usually older men and often metastatic at time of diagnosis
- Usually has a component of conventional SCC
- IHC: p53+, EBV(+/-)

HUMAN PAPILLOMAVIRUS


Capsid Protein L1
Capsid Protein L2
Histone
Genomic DNA
HPV Viral infection
Viral integration
Normal Squamous cell
DNA repair & infection cleared
Affected cell
Chronic infection (transformation)
Apoptosis
Dysplasia
• Genome instability
• Loss of tumor suppressor genes
Carcinoma

Human papillomavirus pathogenesis

HUMAN PAPILLOMAVIRUS PATHOGENESIS

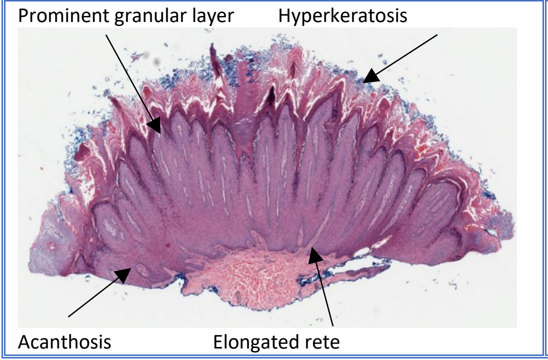
RISK FACTORS

- Exposure to Human Papilloma Virus (HPV) from sexual contact

IMPORTANT FACTS ABOUT HPV

- HPV is a **non-enveloped, circular dsDNA** virus
- Primary oncoproteins: **E6** and **E7**
- **E6 inactivates p53,** which ubiquitinates p53 and undergoes degradation → cell immortalized
- **E7 competes for pRb,** which causes the **release of E2F** and allows for cell cycle to progress → cell proliferation
- **15 "high-risk" types**: **16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82
- **12 "low-risk" types: 6, 11**, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89
- **HPV18** is responsible for **90% of** all HPV-positive oropharyngeal malignancies
- **Many vaccines** exist now for HPV

HPV-RELATED SQUAMOUS NEOPLASMS


Prominent granular layer
Hyperkeratosis
Acanthosis
Elongated rete

VURRUCA VULGARIS

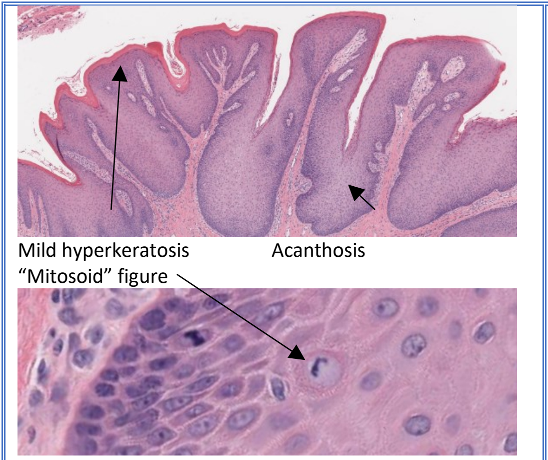
MORPHOLOGY

- **Exophytic** and **papillomatous** squamous proliferation
- Has **hyperkeratosis** and **acanthosis** with elongated "cup-like" rete ridges
- Cytologically bland with **prominent granular layer** and occasional **koilocytes**

OTHER HIGH YIELD POINTS

- Caused by low-risk HPV (e.g., Type 2 and 4)

Path Presenter



MULTIFOCAL EPITHELIAL HYPERPLASIA (HECK'S DISEASE)

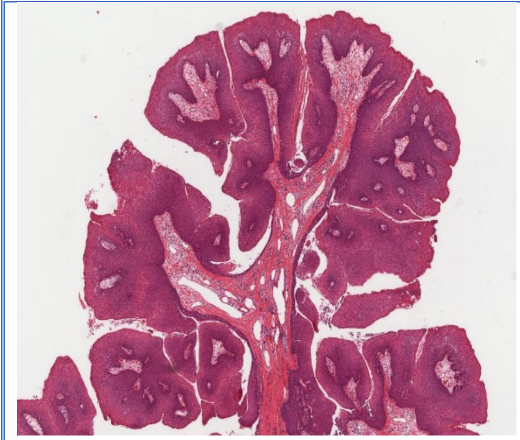
MORPHOLOGY

- Mild **hyperkeratosis**, prominent **acanthosis**, **normal** cell **maturation**
- **"Mitosoid" figures** are hallmark (not often seen in other conditions)
- May show rare koilocytes

OTHER HIGH YIELD POINTS

- Multifocal benign squamous proliferation in **oral cavity**
- Often located on **lips or buccal mucosa** → **multiple papules**
- Most common in **children/adolescent girls**
- Caused by **HPV types 13 or 32**
- Stains are not needed

Path Presenter


Branching fibrovascular cores

SQUAMOUS PAPILLOMA

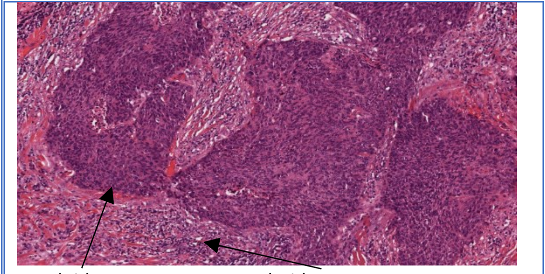
MORPHOLOGY

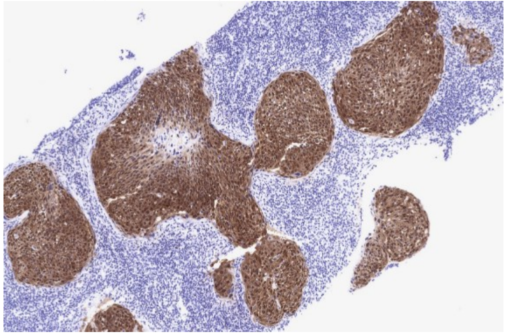
- **Exophytic** squamous proliferation with branching fibrovascular cores
- Can have koilocytes (may be obvious or subtle)

OTHER HIGH YIELD POINTS

- Often solitary, can get through sexual or non-sexual contact,
- Usually associated with **HPV types 6 or 11**
- Malignant transformation is **extremely rare**
- If multiple, especially if young, consider: **Recurrent Respiratory Papillomatosis** (RPR) → multiple, recurrent papillomas in the respiratory tract with high morbidity from obstruction

Path Presenter




"Block-positive" p16

SQUAMOUS CELL CARCINOMA, HPV-POSITIVE

MORPHOLOGY

- **Non-keratinizing squamous cells, high N: C ratios** → basaloid look
- **Frequent mitoses**, **apoptotic figures,** and associated lymphoid stroma
- **No** recognizable **in situ component** or background dysplasia

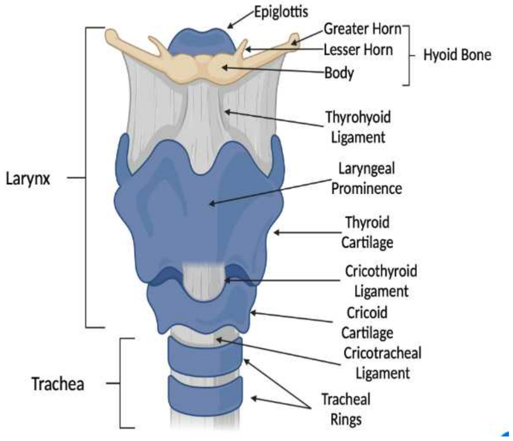
OTHER HIGH YIELD POINTS

- More than 90% are due to **HPV16**
- Significantly **better prognosis** than conventional SCC
- **Strong predilection to oropharynx**: Base of Tongue (BOT) and Tonsils
- Presents at high clinical stage with occult primary and cervical node metastases (often large and cystic)
- Arises in crypts of tonsils → grows and invades as nests
- **Grading is NOT applicable**
- HPV can be detected by: In situ hybridization or PCR
- Diffuse **"block-positive" staining for p16**
- IHC: Positive for CK5/6, p16, CKAE1/AE3

Path Presenter

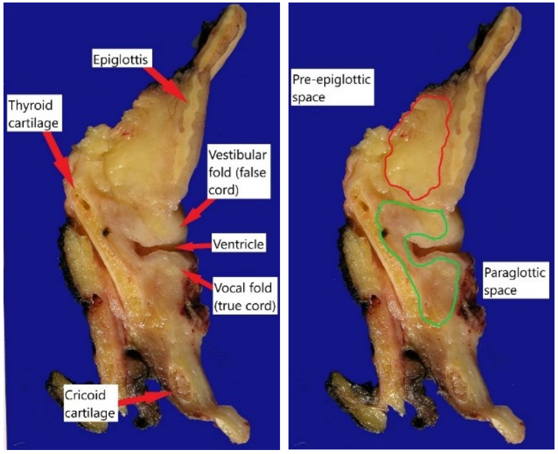
12. HEAD AND NECK PATHOLOGY

LARYNX

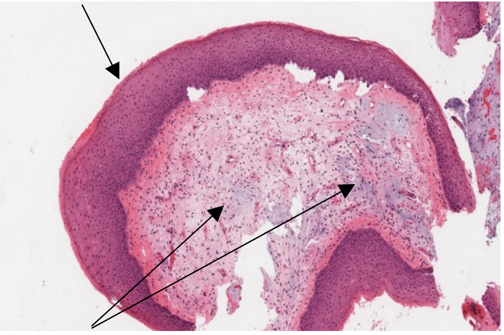

Epiglottis
Greater Horn
Lesser Horn
Body
Hyoid Bone
Thyrohyoid Ligament
Laryngeal Prominence
Thyroid Cartilage
Cricothyroid Ligament
Cricoid Cartilage
Cricotracheal Ligament
Tracheal Rings
Larynx
Trachea

Gross image credits: Cory Nash@iplaywithorgans

ANATOMY - See adjacent diagram


Epiglottis
Thyroid cartilage
Vestibular fold (false cord)
Ventricle
Vocal fold (true cord)
Cricoid cartilage
Pre-epiglottic space
Paraglottic space

Squamous hyperplasia



Fibroblastic myxoid stroma

VOCAL CORD NODULE/POLYP

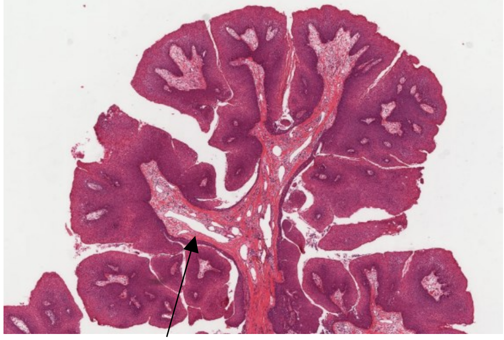
MORPHOLOGY

- **Exophytic growth** with squamous mucosal hyperplasia
- Underlying stroma with **fibroblastic myxoid or hyalinized** appearance

OTHER HIGH YIELD POINTS

- Grossly is a smooth and round appearance
- Patients often present with **hoarseness** as this occurs on true vocal cords
- Occurs in **all ages**
- Most common in **heavy smokers** or patients with chronic GERD

Path Presenter



Branching fibrovascular cores

SQUAMOUS PAPILLOMA

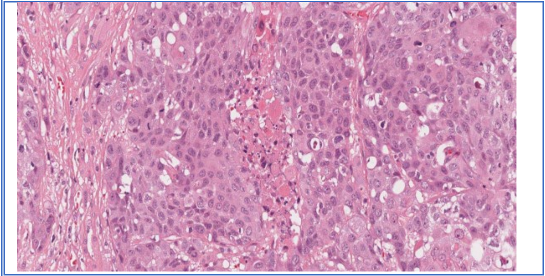
MORPHOLOGY

- **Exophytic** squamous proliferation with branching fibrovascular cores
- Can have **koilocytes** (may be obvious or subtle)

OTHER HIGH YIELD POINTS

- Often solitary, can get through sexual or non-sexual contact
- Usually associated with **HPV types 6 or 11**
- Malignant transformation is **extremely rare**
- IHC: Not needed

Path Presenter



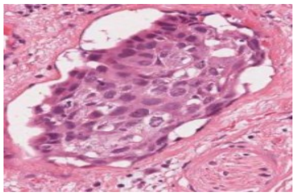
SQUAMOUS CELL CARCINOMA, CONVENTIONAL TYPE

- MORPHOLOGY
- Malignant **epithelial** tumor with **squamous differentiation**
- **Keratinization** (±keratin pearls) and/or **intercellular bridges**
- Irregular nuclear contours, hyperchromatic nuclei, necrosis

OTHER HIGH YIELD POINTS

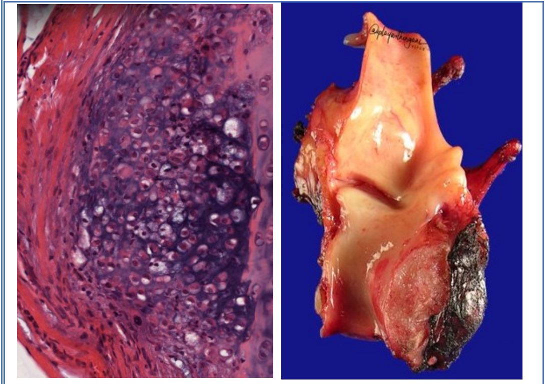
- Grading does NOT depend on keratinization
- Symptoms depend on location: Mass (oral cavity), hoarseness (supraglottic larynx) or dyspnea/stridor (subglottic larynx) etc.

12. HEAD AND NECK PATHOLOGY



Path Presenter

- **Cervical** lymph node **metastasis** (**most adverse prognostic factor**)
- **Extracapsular extension** is a particularly associated with **regional recurrence** and **worse survival**
- More common in males with a Male > female (3:1)
- IHC: CKAE1/AE3+, CK5/6+, p40+, p63+, CK34 beta E12+, p53+ p16-
- Negative HPV DNA/RNA; Negative EBV ISH



Slightly hypercellular with atypical chondrocytes
Gross image credit: Cory Nash@iplaywithorgans

CHONDROSARCOMA

MORPHOLOGY

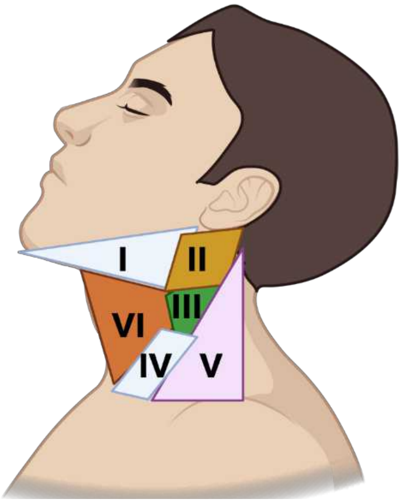
- **Low-grade chondrosarcoma:** Mildly atypical and binucleated chondrocytes within same lacuna, often slightly hypercellular
- **High-grade chondrosarcoma:** Severely atypical or multinucleated chondrocytes with irregular chromatin, conspicuous nucleoli, variable necrosis, and mitotic figures

OTHER HIGH YIELD POINTS

- **Very rare**, most occur in **cricoid cartilage**
- About **20% recur**, and **30% have associated chondroma**
- Clear cell variant has a **loss of 9p22** and **18q22**

Path Presenter

NECK



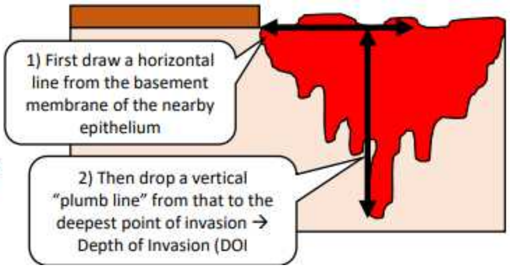
NECK LYMPH NODE LEVELS

LEVELS	NAME	SOURCE OF METASTASIS
I	Submental & Submandibular	Oral and nasal cavities (and submandibular gland)
II	Upper Jugular	Oral & nasal cavities, pharynx, & parotid
III	Mid Jugular	Oral & nasal cavities & pharynx
IV	Lower Jugular	Hypopharynx, cervical esophagus, & larynx
V	Posterior Triangle	Nasopharynx, oropharynx, & scalp
VI	Anterior (Central Compartment)	Thyroid and larynx

Depth of invasion:

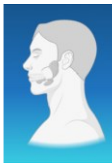
Particularly in oral cavity, predictive of regional lymph node metastasis.

Measure by drawing a horizontal line from the basement membrane of adjacent epithelium and then dropping a "plump line" from this (see →)

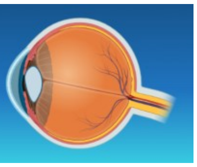


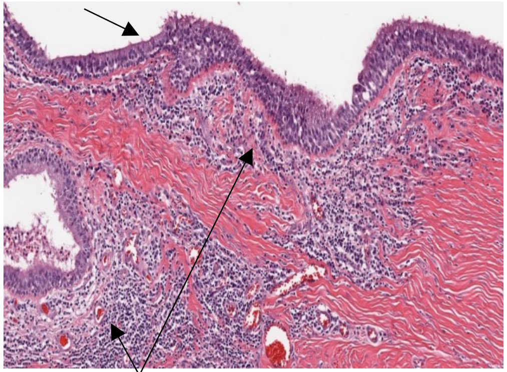
1) First draw a horizontal line from the basement membrane of the nearby epithelium

2) Then drop a vertical "plumb line" from that to the deepest point of invasion → Depth of Invasion (DOI



12. HEAD AND NECK PATHOLOGY




Respiratory epithelium
Mixed inflammatory cells

THYROGLOSSAL DUCT CYST

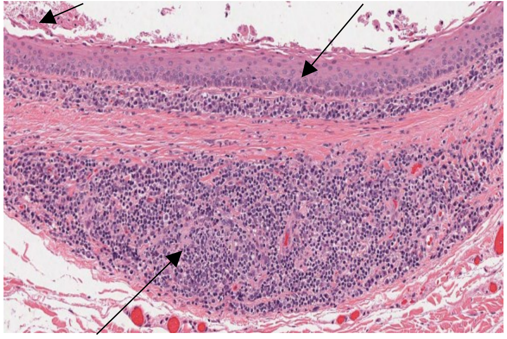
MORPHOLOGY

- Cyst lined by **respiratory epithelium** (can be squamous)
- **Often has thyroid tissue** within cyst wall
- Cyst can be **filled with mucous** (especially if inflamed)

OTHER HIGH YIELD POINTS

- **Congenital anomaly**
- **Midline** lesion occurs anywhere from base of tongue to neck
- Attached to hyoid bone and **moves** during swallowing
- Treatment is surgical (Sistrunk procedure)

Path Presenter


Cyst debris
Squamous lining
Lymphoid aggregates

BRANCHIAL CLEFT CYST

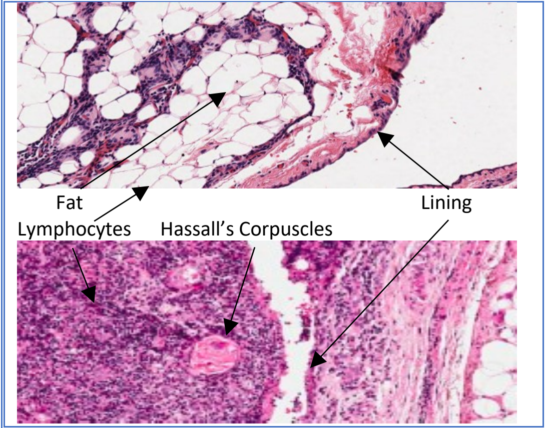
MORPHOLOGY

- Usually lined by **bland squamous epithelium** (rarely glandular lining)
- **Wall** often has **abundant lymphoid aggregates/germinal centers**
- **Cystic debris**

OTHER HIGH YIELD POINTS

- Congenital malformation of branchial apparatus
- Often seen in **young adults** in **lateral neck** and non-tender
- Can have branchial cleft sinuses and fistulas
- In **adults> 50, must exclude metastatic SCC**

Path Presenter


Fat
Lining
Lymphocytes
Hassall's Corpuscles

THYMIC CYST

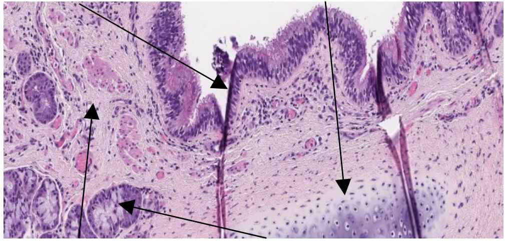
MORPHOLOGY

- Contains **lymphocytes** and other **thymic components,** and fat
- Easiest to find **Hassall's corpuscles** (cuboidal, columnar, or squamous epithelium)

OTHER HIGH YIELD POINTS

- Most common in **kids**
- Usually located in **anterior cervical triangle**
- May not be very cellular and can have **involution**
- May see associated **parathyroid** tissue

Path Presenter


Respiratory-type epithelium
Cartilage
Smooth muscle
Seromucous glands

BRONCHOGENIC CYST

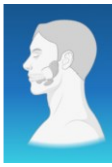
MORPHOLOGY

- Lined by **respiratory-type** epithelium
- Cyst wall contains **seromucous glands**, **cartilage**, **smooth muscle**
- **Scant lymphoid** tissue

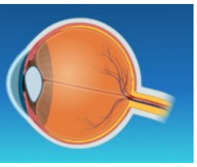
OTHER HIGH YIELD POINTS

- Most common in **kids** can compress nearby structures
- Usually located in **midline**, **near sternum**

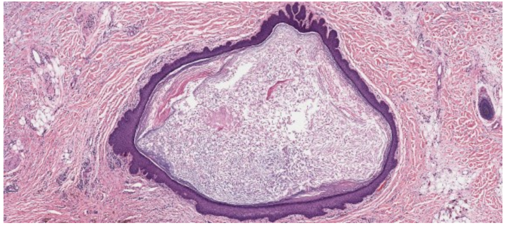
Path Presenter



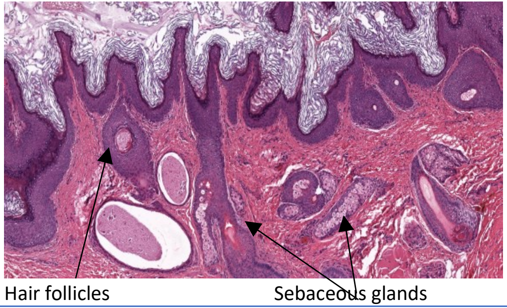
12. HEAD AND NECK PATHOLOGY



Epidermoid Cyst



Dermoid cyst



CUTANEOUS CYSTS (EPIDERMOID & DERMOID CYSTS)

MORPHOLOGY

Epidermoid Cyst:

- Unilocular cyst, lined by **squamous epithelium** with **granular layer**
- Abundant **keratin debris** in lumen (keratin "corn flakes")
- If rupture → acute/granulomatous inflammation

Dermoid Cyst:

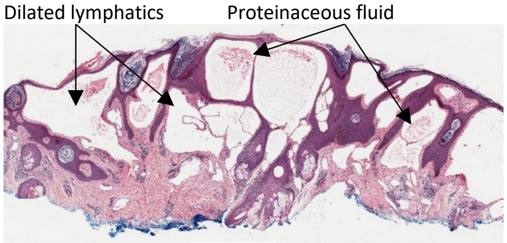
- Unilocular cyst, lined by **squamous epithelium** with granular layer
- Has **associated adnexal structures** (hair follicles or sebaceous glands)
- Abundant keratin debris in lumen (keratin "corn flakes")
- If rupture → acute/granulomatous inflammation

OTHER HIGH YIELD POINTS

- **Epidermoid cyst**: very common in adults
- **Dermoid cysts:** usually on **face of kids** along embryonic closure lines
- Expressed material has a terrible smell noticeable during gross exam

Path Presenter

Epidermoid Cyst   Dermoid Cyst



Path Presenter

LYMPHANGIOMA

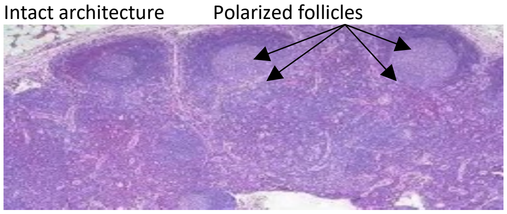
MORPHOLOGY

- Localized collections of **dilated lymphatic channels** filled with **proteinaceous fluid**
- Walls have variable thickness
- Can have smooth muscle and/or fibrous tissue in wall

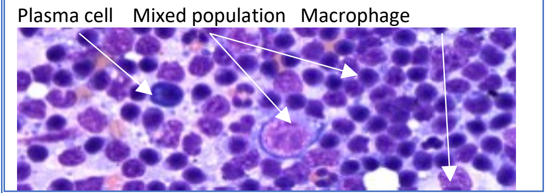
OTHER HIGH YIELD POINTS

- Most common in **kids/infants** on **posterior head/neck**
- Can be associated with Turner's Syndrome ("cystic hygroma")
- **IHC: D2-40+**, CD31+; PROX1+; variable CD34

INFECTIOUS LESIONS



FNA aspirate (Diff-Quik)



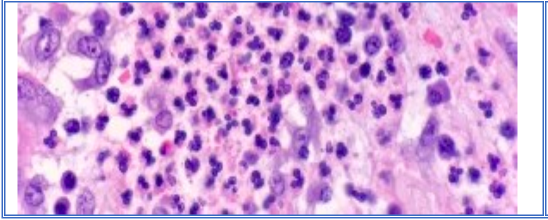
REACTIVE LYMPHOID HYPERPLASIA

MORPHOLOGY

- Proliferation/collection of **heterogeneous lymphoid cells**
- Intact nodal architecture
- Separated follicles with "open" sinuses
- Polarized germinal centers/mantle zones with prominent mitosis

OTHER HIGH YIELD POINTS

- On FNA, aspirate very cellular with mixture of lymphoid cells, which display a maturation pattern and predominance of small lymphocytes
- Frequently have plasma cells and "tingible body" macrophages
- **Benign (Reactive) IHC:** B-Cell Zones (CD19, CD20+), T-Cell Zones (CD3, CD4, CD8+) and immunoblasts (CD20, CD30+), Germinal centers **BCL2 negative**
- **Malignant (Neoplastic) IHC:** Germinal centers are **BCL2 positive**
- Consider flow cytometry if bilateral lymphadenopathy or B-symptoms



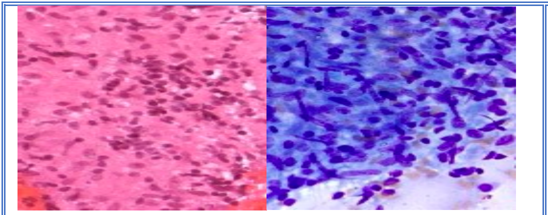
ABSCESS

MORPHOLOGY

- Large **collections of neutrophils** (some are degenerating)
- **Necrosis** and **fibrin** ("Fibrinopurulent debris")
- Macrophages, bacteria, foreign material, granulation tissue

OTHER HIGH YIELD POINTS

- Associated with **poor dentition**



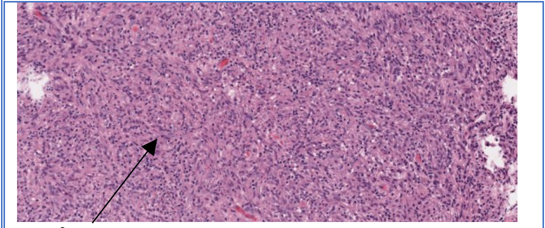
GRANULOMAS

MORPHOLOGY

- **Well-formed** collections of **histiocytes** and **multinucleated cells**

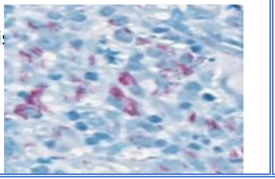
OTHER HIGH YIELD POINTS

- Main differentials **Non-necrotizing: Sarcoidosis**
- Main differentials **Necrotizing: Mycobacterium tuberculosis**, **Bartonella henselae**, **Fungal** infections (rare)



Storiform pattern

Abundant AFB positive organi



MYCOBACTERIAL SPINDLE CELL PSEUDOTUMOR

MORPHOLOGY

- Cellular pseudoneoplastic proliferation of storiform spindled cells
- Effacement of lymph node architecture

OTHER HIGH YIELD POINTS

- Presents as a **firm mass** and almost exclusively seen in **HIV**
- Usually caused by ***M. avium-intracellulare*** with **positive AFB stain**
- **IHC:** CD68+, vimentin+, S100 (±), Desmin(±), SMA(±) , (-) CD31(-), CD34(-)
- **Treatment:** treat infection

Path Presenter

HPV TESTING OF HEAD AND NECK

HIGH YIELD POINTS

- **p16 is an adequate surrogate** marker for High-risk (HR) HPV infection
- If **p16 positive ≥70% nuclear and cytoplasmic staining** with classic **non-keratinizing morphology**→ "Metastatic SCC, HPV-positive."

CHARACTERISTIC	HPV-POSITIVE SCC	HPV-NEGATIVE SCC
Median age	~50 years	~65 years
Risk Factors	Sexual behavior	Smoking & Alcohol
Background Dysplasia	Rare	Frequent
Morphology	Commonly non-keratinizing with high N:C ratio	Conventional, often keratinizing
Grading	Not applicable	Applicable
P16 IHC	"Block" positive	Negative
Lymph node metastasis	Frequently cystic	Uncommon to be cystic
Postulated origin	Reticulated epithelium of invaginated crypts	Surface epithelium
3-Year survival	~80%	~60%

Adapted from: WHO Classification of Head and Neck Tumors (2017).

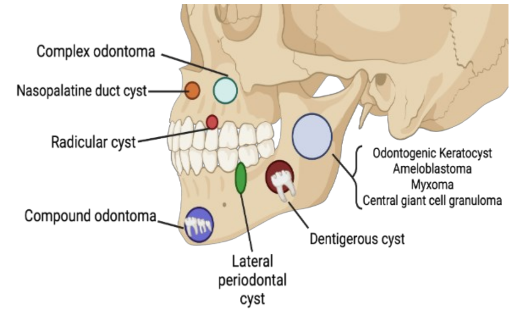
OTHER NEOPLASMS TO CONSIDER IN A NECK MASS

Organ	Diagnosis
Thyroid	Papillary thyroid carcinoma, Follicular thyroid carcinoma, Medullary thyroid carcinoma, Anaplastic carcinoma
Soft tissue	Lipoma (and variants), Schwannoma, Fibromatosis, Nodular Fasciitis, Paraganglioma, Elastofibroma, Nuchal-type fibroma, Perineurioma, Synovial sarcoma, Chordoma, Liposarcoma, Rhabdomyosarcoma
Systemic Metastases	Melanoma, Lung carcinoma, Breast carcinoma
Salivary gland	Pleomorphic adenoma, Warthin Tumor (papillary cystadenoma lymphomatosum), Adenoid cystic carcinoma, Mucoepidermoid carcinoma, Salivary duct carcinoma
Hematopoietic	Lymphoproliferative disorders

12. HEAD AND NECK PATHOLOGY

JAW LESIONS

JAW LESIONS


Complex odontoma
Nasopalatine duct cyst
Radicular cyst
Odontogenic Keratocyst
Ameloblastoma
Myxoma
Central giant cell granuloma
Compound odontoma
Dentigerous cyst
Lateral periodontal cyst

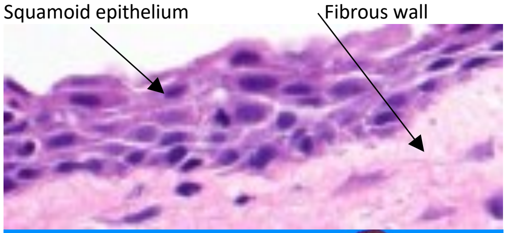
Created with biorender.com by Terrance Lynn, MD

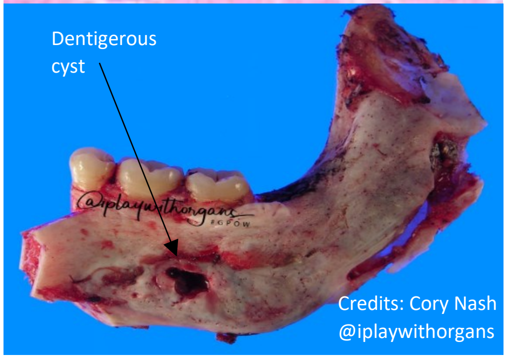
GENERAL

MORPHOLOGY

- **Diverse array** of lesions can arise in the jaw
- Many lesions associated with odontogenesis
- Can involve epithelial and/or mesenchymal elements
- Lesions may be cysts, tumors, or reactive
- Odontogenic tumors are *relatively rare*; less than 1% of oral tumors
- Can be **locally aggressive** and have a high rate of recurrence
- **Radiographic and clinical correlations are essential** for the diagnosis
- Location in relation to teeth is important for odontogenic tumors

DEVELOPMENTAL CYSTS


Squamoid epithelium
Fibrous wall


Dentigerous cyst

Credits: Cory Nash @iplaywithorgans

DENTIGEROUS CYSTS (FOLLICULAR CYST)

MORPHOLOGY

- Wall of **fibrous tissue with regular squamoid epithelium** (sometimes glandular)
- Variable **inflammation**, **cholesterol clefts**, epidermal hyperplasia

OTHER HIGH YIELD POINTS

- Envelops the crown of an unerupted tooth
- **Most common around impacted teeth and in teenagers**
- Often **found incidentally** on X-ray looking for missing tooth
- **Treatment:** excision

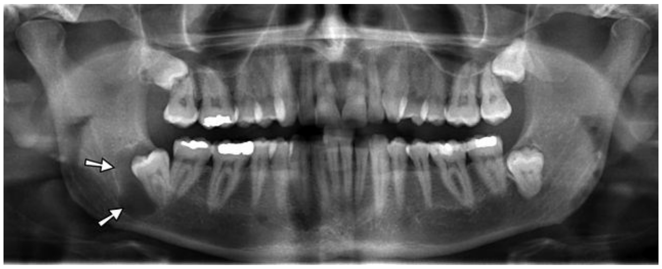
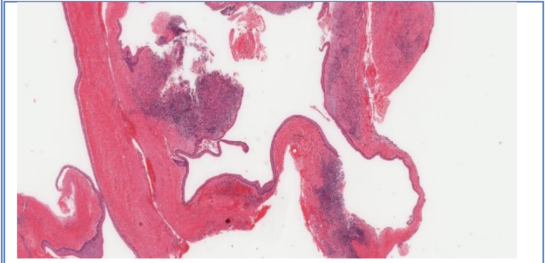
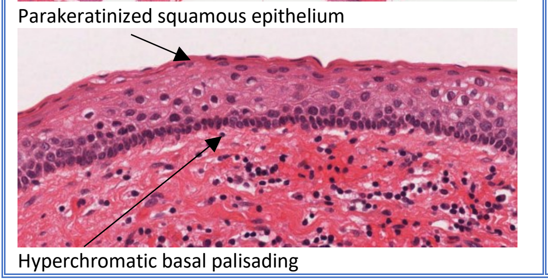


Photo provided by: JBarta on Wikimedia




Parakeratinized squamous epithelium
Hyperchromatic basal palisading

ODONTOGENIC KERATOCYST (OKC)

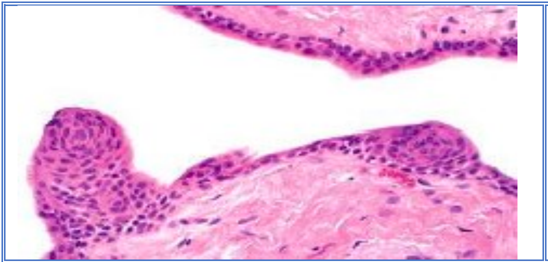
MORPHOLOGY

- Thin, **parakeratinized squamous epithelium**
- **Basal palisading** hyperchromatic cells

OTHER HIGH YIELD POINTS

- Second most common odontogenic cyst
- Occur over a broad age range, majority in the mandible
- Usually incidental painless finding
- Can see satellite cysts and islands in the wall
- If multiple or young patients → **Gorlin syndrome** (Nevoid basal cell carcinoma syndrome) → germline PTCH1 mutations
- **PTCH1 mutations** are also **seen in sporadic** OKC
- High rate of recurrence (~25%)

Path Presenter



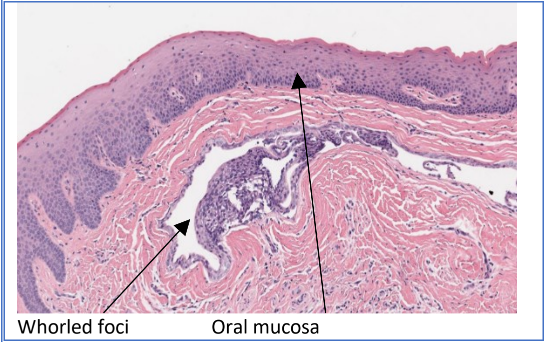
LATERAL PERIODONTAL CYST

MORPHOLOGY

- **Non-keratinizing squamous epithelium**
- Cyst epithelium usually **only 1-2 cells** thick with focal whorled areas

OTHER HIGH YIELD POINTS

- Uncommon but seen in adults in mandible
- Arises from **lateral aspect** or **between roots of erupted teeth**
- Multicystic variant → Botryoid odontogenic cyst



GINGIVAL CYST

MORPHOLOGY

- **Non-keratinizing squamous epithelium**
- Cyst epithelium usually only **1-2 cells thick** with **focal whorled areas**

OTHER HIGH YIELD POINTS

- Most common in infants (but not biopsied → spontaneously resolved)
- Occur just below oral mucosa

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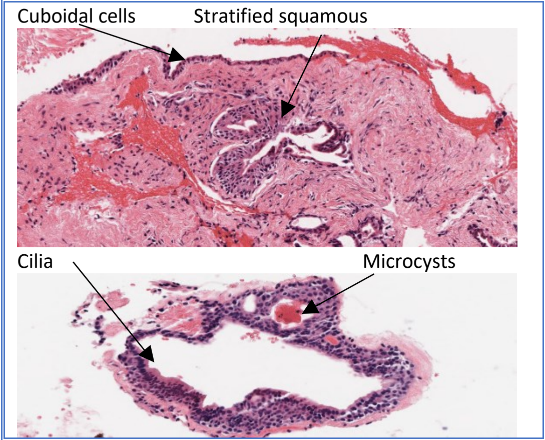


GLANDULAR ODONTOGENIC CYST

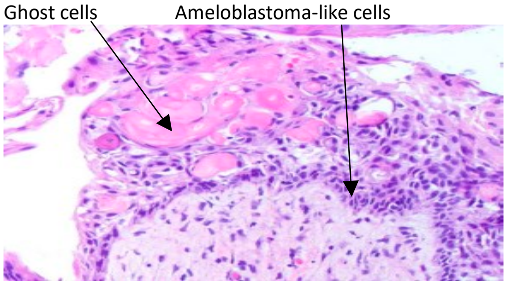
MORPHOLOGY

- **Variable epithelium** from 2-3 cells to thicker stratified squamous epithelium
- Can see **cuboidal cells, microcysts, apocrine metaplasia, clear cells, tufting, mucous cells, and cilia**

OTHER HIGH YIELD POINTS

- Cyst with epithelial cells that simulate salivary gland differentiation
- **Rare**, often asymptomatic, in the mandible, high rate of recurrence
- **Associated with multiple roots of teeth**
- Must exclude mucoepidermoid carcinoma

Path Presenter



CALCIFYING ODONTOGENIC CYST (TUMOR)

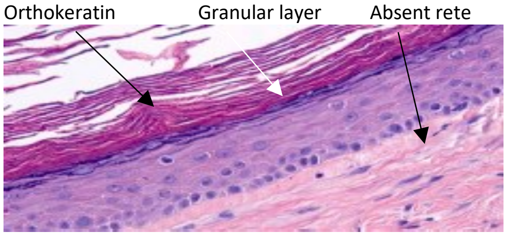
MORPHOLOGY

- **Ameloblastoma-like cells** (basal layer with palisading columnar cells)
- Often contains focal accumulations of **"ghost" cells**, which can **calcify**

OTHER HIGH YIELD POINTS

- Can be associated with odontoma
- Recurrence is rare

Path Presenter



ORTHOKERATINIZED ODONTOGENIC CYST

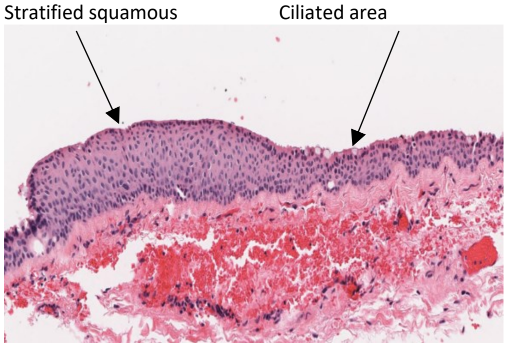
MORPHOLOGY

- Odontogenic cyst lined by **orthokeratinized squamous** epithelium
- **Prominent granular** layer, **absence** of **rete ridges, Fibrous wall**

OTHER HIGH YIELD POINTS

- Most commonly seen in the **mandible** and arise from dental lamina/remnants
- Very low risk of recurrence (1-2%)

12. HEAD AND NECK PATHOLOGY



NASOPALATINE DUCT CYST

MORPHOLOGY

- Lined mostly by **stratified squamous epithelium**
- May see focal cuboidal, columnar, or ciliated areas

OTHER HIGH YIELD POINTS

- Non-odontogenic cyst in adults (4-5th decade, mostly male)
- Arises in midline of **anterior maxilla** of hard palate
- Hyperkeratotic features have higher recurrence rate

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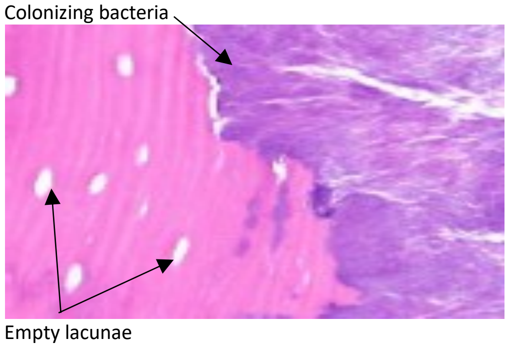
REACTIVE/INFLAMMATORY LESIONS



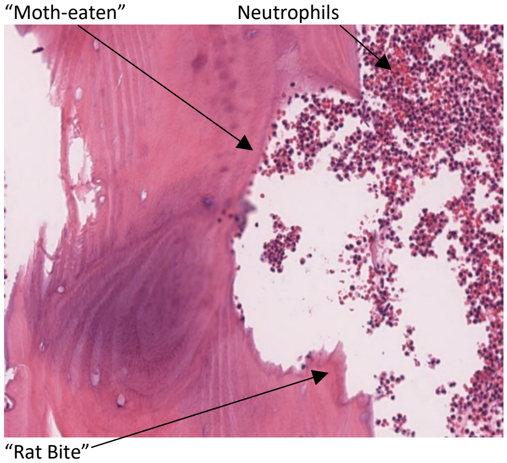
OSTEONECROSIS (AVASCULAR BONE NECROSIS)

MORPHOLOGY

- **Necrotic, devitalized bone** (empty lacunae)
- Fibrosis, fibrinous exudate, inflammation
- Often with bacterial colonization

OTHER HIGH YIELD POINTS

- Overlapping histologic findings with infection/trauma
- Presents as pain, can have a foul smell
- Common causes: Radiation therapy (osteoradionecrosis) and Bisphosphonates
- Most common when radiation exposure >60 Gy or intensity-modulated radiotherapy



OSTEOMYELITIS (ACUTE AND CHRONIC)

MORPHOLOGY

- **Acute Osteomyelitis:** Neutrophilic inflammation with bone destruction, edema, and fibrosis
- **Chronic Osteomyelitis:** Plasma cells and lymphocyte-rich inflammation with bone destruction, edema, and fibrosis

OTHER HIGH YIELD POINTS

- Can see **necrotic bone** with **empty lacunae** → **osteonecrosis**
- Can have **brisk osteoclast activity**
- Bone often appears **"moth eaten"** with lots of **"rat bites"**
- Often secondary to **poor dentition or dental extractions**
- Can also result from hematogenous spread

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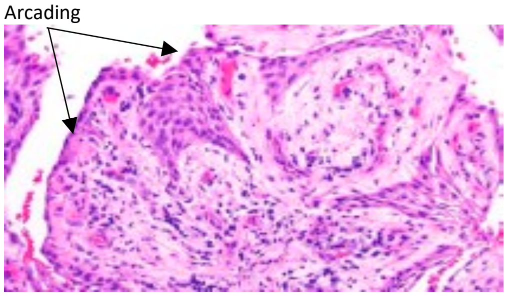


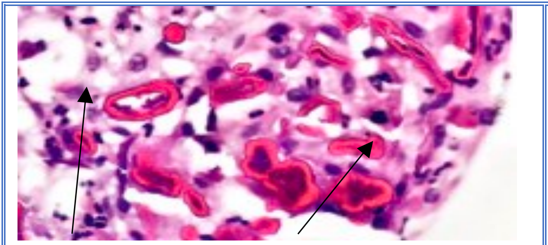
RADICULAR CYST (PERIAPICAL CYST)

MORPHOLOGY

- Wall of inflamed fibrous/granulation tissue
- Non-keratinizing hyperplastic **"arcading" squamous epithelium**
- Often foamy macrophages and cholesterol clefts
- Eosinophilic **"Rushton" bodies** (nonspecific)
- Cyst lumen contains thin straw-colored fluid

OTHER HIGH YIELD POINTS

- **Most common cyst of the jaw**
- **Inflammatory** odontogenic cyst **associated with non-vital teeth**



- Formed from proliferating tooth root sheath after pulp necrosis (usually due to dental caries)
- **“Rushton” bodies**: eosinophilic hyaline bodies with variable shapes but are uncommon

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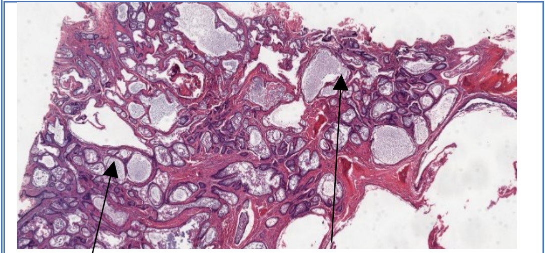
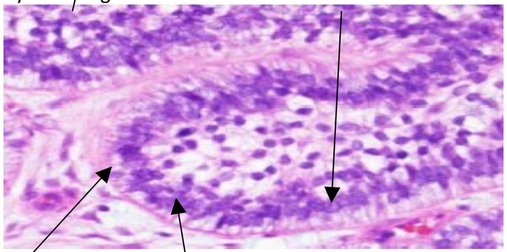
EPITHELIAL ODONTOGENIC TUMORS





AMELOBLASTOMA

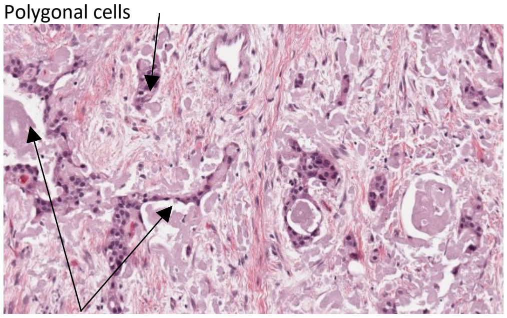
MORPHOLOGY

- Columnar/cuboidal palisading cells with hyperchromatic nuclei and reverse polarity
- Central loosely arranged stellate cells resembling stellate reticulum
- Can undergo cystic change

OTHER HIGH YIELD POINTS

- **Most common odontogenic tumor** (excluding odontoma)
- Expansile growth
- **Tendency to recur** if not completely resected
- **Unicystic type**→ occurs as a single cystic cavity and associated with impacted tooth
- **Extraosseous/Peripheral type** → Soft tissues of gingiva
- **Metastasizing Ameloblastoma** → Rare but metastasizes
- **MAPK** pathway activation with frequent ***BRAF* V600E**
- IHC: SOX10 negative; stains rarely needed because of uniqueness

Path Presenter



CALCIFYING EPITHELIAL ODONTOGENIC TUMOR (CEOT)

MORPHOLOGY

- Polygonal cells with abundant cytoplasm and intercellular bridges
- Abundant pink amyloid
- Calcifications often (concentric = “Liesegang rings”)
- Pleomorphic and giant nuclei with low mitotic rate

OTHER HIGH YIELD POINTS

- **Benign and rare**
- **Infiltrative but less aggressive** than Ameloblastoma
- **IHC:** Keratins+, Congo Red+

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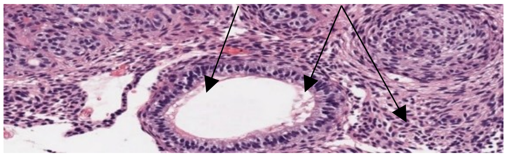
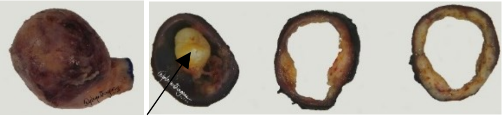



Encapsulated nodular lesion with unerupted tooth
Gross image credits: Cory Nash@iplaywithorgans

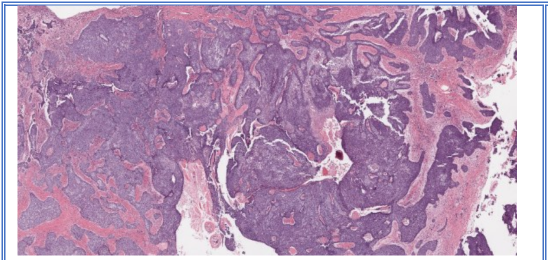
ADENOMATOID ODONTOGENIC TUMOR

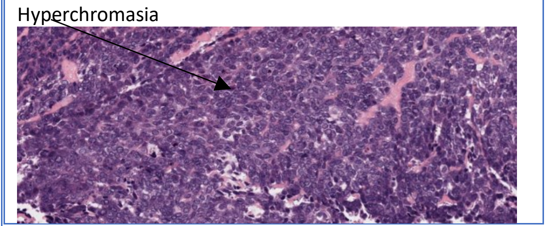
MORPHOLOGY

- Encapsulated and multinodular
- Minimal stroma
- Spindled epithelial cells
- Rosette or duct-like spaces with outward-oriented nuclei

OTHER HIGH YIELD POINTS

- Benign tumor
- **Most common in teens/young adults**
- Often in **maxilla with unerupted teeth**
- **Low recurrence** rate with enucleation





AMELOBLASTIC CARCINOMA

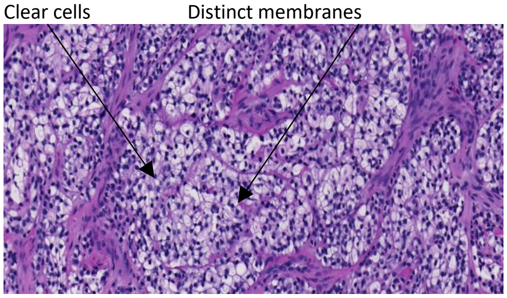
MORPHOLOGY

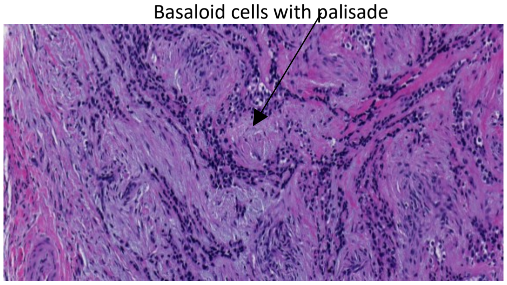
- Ameloblastoma histology
- **Cytologically malignant** cells
- Nuclear pleomorphism, mitoses, hyperchromasia
- Often with vascular/perineural invasion
- Variable necrosis (the usual findings of malignancy)

OTHER HIGH YIELD POINTS

- Very rare tumor
- Frequent **BRAF mutations**
- **Multimodal treatment,** 20% survival with metastasis

Path Presenter





CLEAR CELL ODONTOGENIC CARCINOMA

MORPHOLOGY

- **Sheets and islands of vacuolated clear cells** (glycogen-rich)
- Distinct cell membranes and irregular small dark nuclei
- Cells often basaloid at tumor periphery
- Stromal desmoplasia

OTHER HIGH YIELD POINTS

- **Rare, <100 cases ever reported**
- **Presents as pain and loose teeth**
- Most common in **5-6th decade**
- More common in **females**
- Most common site is **mandible**
- Metastasis to **lung, bone, lymph nodes**
- Survival: ~70-80% at five years
- **Recurrence: Common** → 80% in curetted/enucleation
- IHC: CKAE1/AE3+, EMA+
- Molecular: **EWSR1-ATF1 translocation** → **t(12;22)(q13;q12)**

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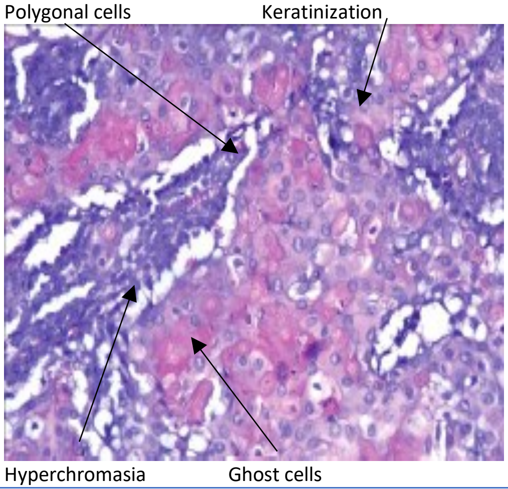


GHOST CELL ODONTOGENIC CARCINOMA

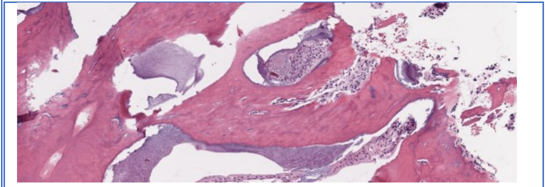
MORPHOLOGY

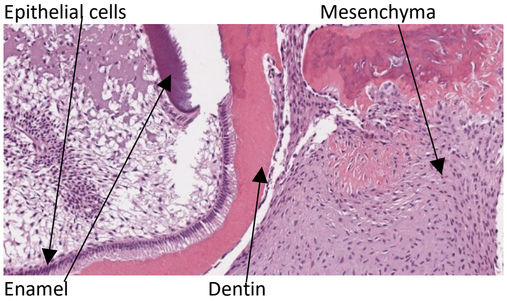
- Polygonal cells with abundant cytoplasm and intercellular bridges
- **Ghost cells**
- Aberrant **keratinization**
- **Hyperchromasia**
- Variable nuclear morphology

OTHER HIGH YIELD POINTS

- **Rare, <50 cases ever reported**
- Mostly seen in Asia
- **Male predominance** mostly in **maxilla**
- IHC: Pancytokeratin+, p63+, increased Ki-67,
- Sometimes aberrant p53 expression

ODONTOGENIC TUMORS WITH MESENCHYMA COMPONENTS





ODONTOMA

MORPHOLOGY

- Mixed epithelial and mesenchymal components
- Dentin and enamel

OTHER HIGH YIELD POINTS

- **Most common odontogenic tumor occurs in any tooth-bearing area**
- **No** sex predilection **and** usually seen in the **first two decades**
- **Compound odontoma:** multiple rudimentary teeth (with dentin, cementum, enamel, pul)
- **Complex odontoma:** irregular mass of tooth components (with no anatomic resemblance to a tooth)
- Associated with **Gardner Syndrome** (FAP gene)

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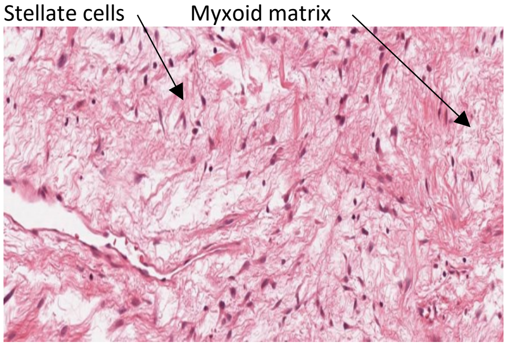

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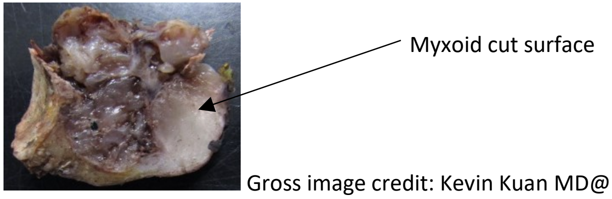
ODONTOGENIC MYXOMA

MORPHOLOGY

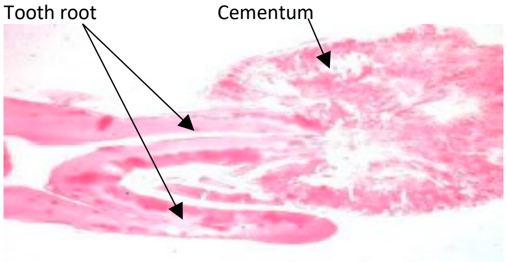
- **Stellate to spindled cells** in abundant myxoid matrix
- May see rare odontogenic epithelium

OTHER HIGH YIELD POINTS

- **Benign** and more common in **females**
- Mostly in 2nd to 4th decades and >2/3 occur in mandible
- IHC: Positive for ORM1, SMA



Gross image credit: Kevin Kuan MD@kkuanMD



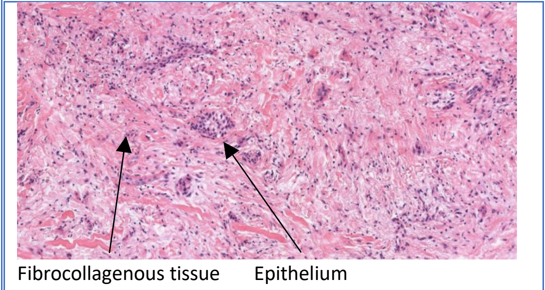
CEMENTOBLASTOMA

MORPHOLOGY

- Cementum-like tissue deposited directly on a tooth root
- Often have fibrovascular cores
- Trabeculae lined with swollen osteoblasts

OTHER HIGH YIELD POINTS

- **Benign** and seen in males and females < 25 years old
- Often stops growing and becomes calcified nodule



ODONTOGENIC FIBROMA

MORPHOLOGY

- Fibrous tissue with odontogenic epithelium and calcifications

OTHER HIGH YIELD POINTS

- **High recurrence** seen in more than half of cases
- **IHC:** CKAE1/AE3+, **CK19+, CK14+**

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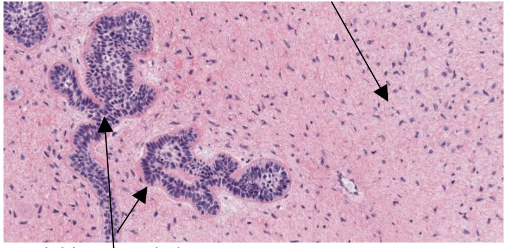
12. HEAD AND NECK PATHOLOGY


Dense collagen stroma
Ameloblastic epithelium

AMELOBLASTIC FIBROMA

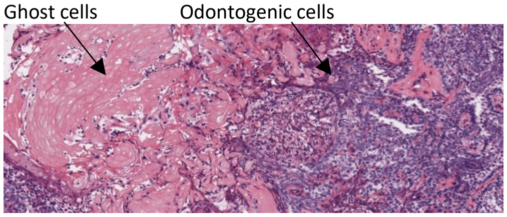
MORPHOLOGY

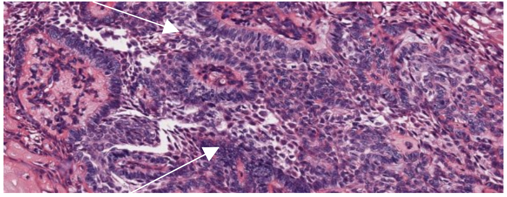
- **Ameloblastic-like** epithelium with “**piano key**” look and papillae
- **Collagenous stroma**

OTHER HIGH YIELD POINTS

- **Benign** and **rare**
- Seen in the first two decades

Path Presenter


Ghost cells
Odontogenic cells


Ameloblastic like epithelium
Stellate cells

DENTINOGENIC GHOST CELL TUMOR

MORPHOLOGY

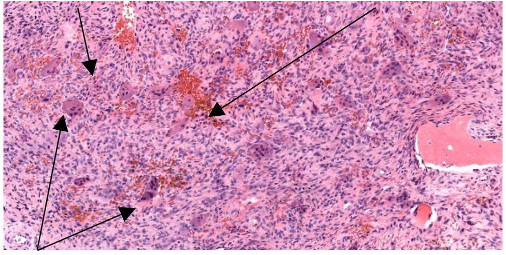
- Islands and nests of **odontogenic epithelium**
- Can have **ameloblastic-like epithelium** with **stellate cells**
- **Anucleate cells** with pale eosinophilic cytoplasm (**Ghost cell**)

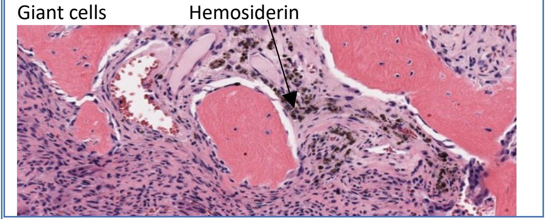
OTHER HIGH YIELD POINTS

- **Benign** and **rare**
- Can have squamous differentiation
- Often in posterior maxilla and mandible
- Presents as asymptomatic swelling
- **IHC:** Beta catenin+, LEF1+ (both non-specific)

Path Presenter

GIANT CELL-RICH TUMORS


Mononuclear spindle cells
Hemorrhage
Giant cells


Hemosiderin

CENTRAL GIANT CELL GRANULOMA

MORPHOLOGY

- Mononuclear **spindle-shaped/polygonal cells**
- **Osteoclast-type giant** cells
- **Vascular background** with **hemorrhage** & **hemosiderin**

OTHER HIGH YIELD POINTS

- **Previous nomenclature:** Reparative Giant Cell Granuloma
- **Benign** neoplasm that is often associated with **trauma**
- **Usually in females under age 20** and most common in **mandible**
- **Radiological findings:** radiolucent and multilocular
- **Gross examination:** cystic bone lesion
- Localized (but sometimes aggressive) **osteolytic** lesion
- Treatment: Curettage
- Differential diagnosis: Aneurysmal bone cyst

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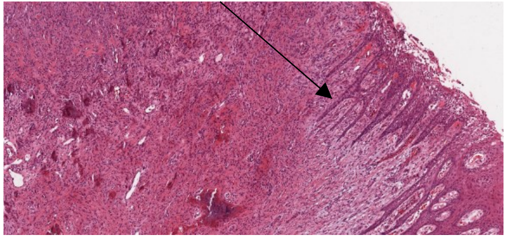

Pseudoepitheliomatous hyperplasia
Immature bone
Spindle/polygonal cells

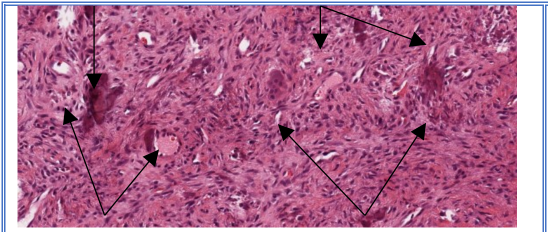
PERIPHERAL GIANT CELL GRANULOMA (GIANT CELL EPULIS)

MORPHOLOGY

- Mononuclear **spindle-shaped/polygonal cells**
- Osteoclast-type **giant cells** and **immature** bone
- **Vascular background** with **hemorrhage** & **hemosiderin**
- Can get **pseudoepitheliomatous hyperplasia** of squamous mucosa

OTHER HIGH YIELD POINTS

- **Previously nomenclature**: Giant Cell Epulis
- **Benign**, **extraosseous** lesion occurring in gingiva and alveolar mucosa


Vascular background
Giant cells

- **Most common oral** giant cell lesion **caused by chronic irritation**
- Usually in **females** and seen **in the 3rd to 5th decade**
- **Treatment:** Remove the source of irritation +/- Curettage
- Will **recur if irritation** source persists

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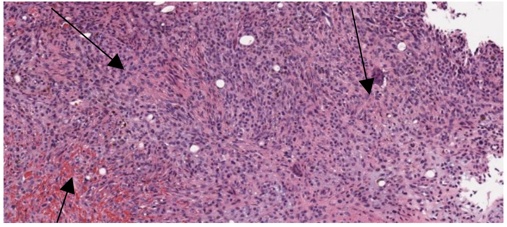
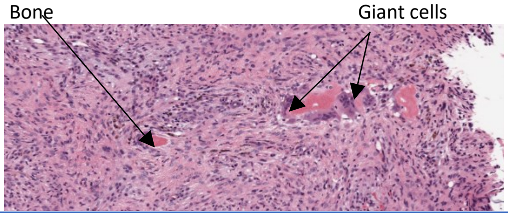

Spindle cells
Giant cells
Hemorrhage


Bone
Giant cells

CHERUBISM

MORPHOLOGY

- **Nonspecific morphology** with spindle-shaped/polygonal cells
- Osteoclast-type giant cells with fibrovascular background
- Hemorrhage & hemosiderin

OTHER HIGH YIELD POINTS

- **Indistinguishable** from Peripheral and Central Giant Cell Granuloma
- Inheritance: **Autosomal Dominant**
- Mutation: activating mutations of **SH3B2** on chromosome **4p16.3**
- **Symmetrical expansion** of the **maxilla** and **mandible**
- Presents in **childhood** with a "heavenly gaze" → (big cheeks, upward gaze) and is reminiscent of Cherubs in Renaissance paintings
- Often **regresses** in **adulthood**

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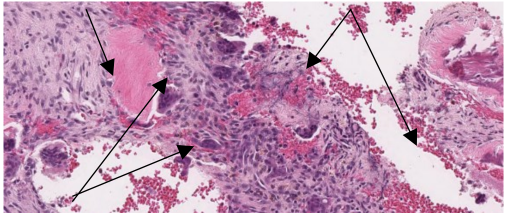
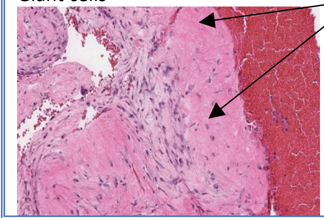

Woven bone
Blood filled spaces
Giant cells


Fibrous septae

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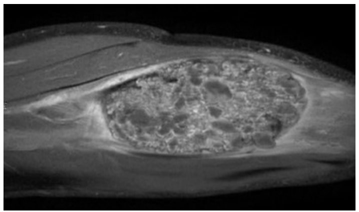
ANEURYSMAL BONE CYST (ABC)

MORPHOLOGY

- Cystic lesion with osteoclast-type giant cells and woven bone
- Blood-filled spaces lined by fibrous septae

OTHER HIGH YIELD POINTS

- **Rare in jaw, usually young patients**
- **Molecular: 17p13.2 locus abnormality and Fusion of *USP6*** with various partners (*CDH11* most common)



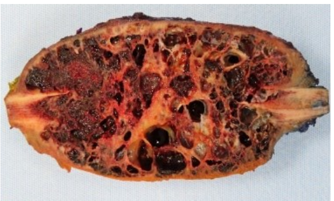
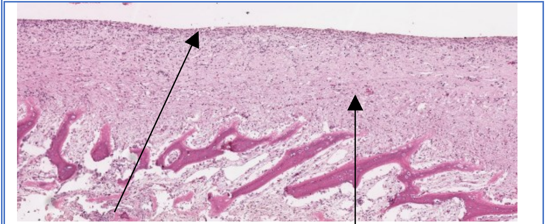


Image credit: Kevin Kuan MD @Kkuan


No epithelial lining
Fibrous wall

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SIMPLE BONE CYST (UNICAMERAL BONE CYST)

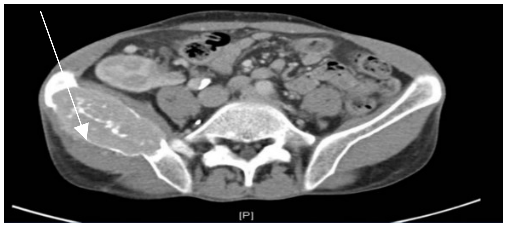
MORPHOLOGY

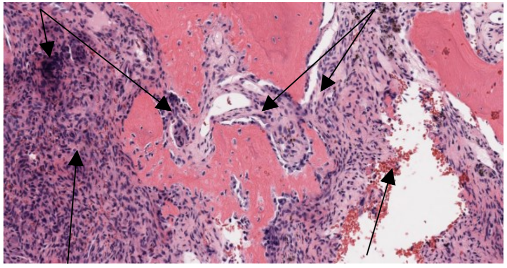
- Unilocular **cystic lesion** with **serosanguinous fluid**
- Fibrous wall **lacking an epithelial lining**

OTHER HIGH YIELD POINTS

- **Often asymptomatic**
- **Male** > female (~3:1) and occurs in **first two decades**
- Local recurrence <20%
- **Favorable prognostic factors:** Age >5, small cyst size, absence of pathologic fracture, not near epiphysis

12. HEAD AND NECK PATHOLOGY





BROWN TUMOR OF HYPERPARATHYROIDISM

MORPHOLOGY

- Marked **osteoclastic** (giant cells rich) **proliferation** in **lobular** pattern
- Vascular **fibroblastic stroma** with **hemorrhage** and **hemosiderin**
- Tunneling **resorption**

OTHER HIGH YIELD POINTS

- **Impossible** to distinguish from central giant cell granuloma
- **Uncommon** metabolic bone disorder due to early diagnosis today
- Typically, in **older** individuals, **female** > male (3:1)
- Knowing **PTH level** is critical as well as other contributing diseases
- **Elevated calcium and alkaline phosphatase levels**
- Often with **increased urinary calcium** excretion
- Can be from **primary, secondary, or tertiary hyperparathyroidism**
- **Incidence: ~2% in primary** and **~15%** in **secondary**
- **Grossly: brown** from hemorrhage, hemosiderin, and vascularity

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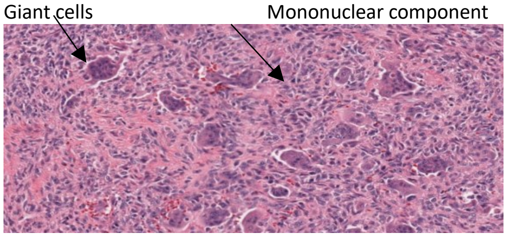

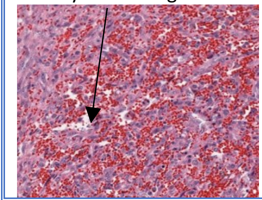

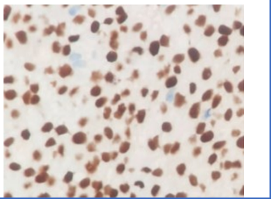

GIANT CELL TUMOR OF BONE (GCTB)

MORPHOLOGY

- The proliferation of large osteoclasts with oval to spindled mononuclear cell neoplastic component
- Often with reactive bone formation and/or aneurysmal change

OTHER HIGH YIELD POINTS

- Rare in jaw, presents as **bone pain**, **pathologic fracture** (~10%)
- **Risk factors:** Paget's (Bone), Gorlin-Goltz syndrome
- **X-Ray findings**: **Well-defined lytic lesion** with **non-sclerotic margin**
- **Molecular:** G34W mutation of *H3F3A* gene, *Wnt* activation,
- **IHC: H3G34W+,** p63+, SALL4+, SATB2+

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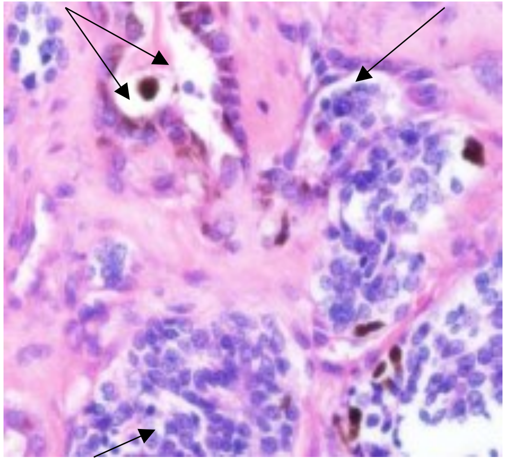
BONE & CARTILAGE TUMORS WITH SPECIAL PREDILECTION FOR THE JAW



MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY

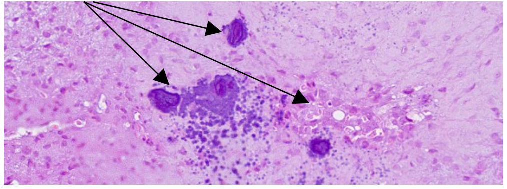
MORPHOLOGY

- **Biphasic tumor** with small **(round cell) neuroblast-like** cells surrounded by larger **melanin-producing epithelioid cells**
- Cells arranged in alveolar structures (See image) with cords and trabeculae set in a **fibrous stroma**

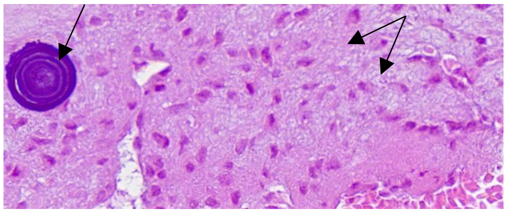
OTHER HIGH YIELD POINTS

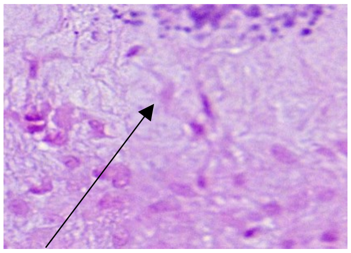
- **Rare** and **benign, occurs in 1st year of life,** nearly all cases in infants
- **Causes deformity** due to rapid enlargement → **locally aggressive**
- Gross appearance: **Blue-gray** from melanin pigmentation; lobulated
- Hypothesized to be of **neural crest origin** → Elevated VMA levels
- **Head/Neck ~65% of cases**; other common: testis & epididymis
- Usually **cured** by **complete excision**
- **IHC: Small round cell** → Synaptophysin+, NSE+, GFAP+, CD57+; **Epithelioid cells** → Synaptophysin+, CKAE1/AE3+, HMB45+;
- **Rare** reports: ***CDNK2A, RPLP1-C19MC* fusion, *BRAF* V600E** mutations

Mineral deposits



Psammomatous calc





Sharpey's Fibers

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OSSIFYING FIBROMA

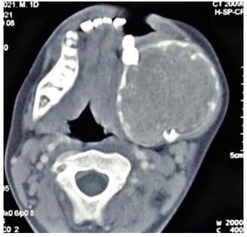
MORPHOLOGY

- Stromal **fibroblastic cells** with **nuclear hyperchromasia**
- Matrix is composed of **woven and lamellar bone** islands
- **Calcification** (+/- psammomatous), **cementum-like** (mineral) deposits
- **"Sharpey's fibers"** → radially projecting collagen fibers from deposits

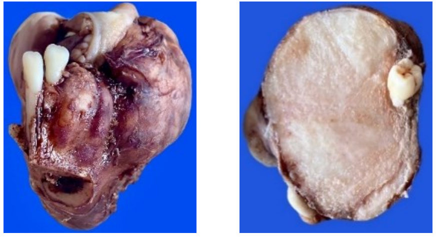
OTHER HIGH YIELD POINTS

- **Benign**, **painless,** and **slow**-growing mass in jaw
- **Syndromic or inherited:** Familial gigantiform cementoma, Gnatho-diaphysial dysplasia (GD), Hyperparathyroidism jaw tumor syndrome (HJTS)
- **Subtypes:** Juvenile (psammomatoid, trabecular), Cemento-ossifying
- **Molecular:** No *GNAS* mutation; *GDD1* mutation in GD (11p14.3);*CDC73* (1q31) in HJTS
- Radiographically radiopaque or radiolucent expansile lesions
- Macroscopically **well-defined encapsulated** lesion

Radiopaque expansile lesion

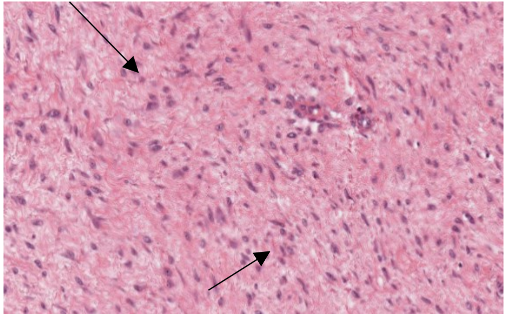


Well-defined encapsulated lesion



Credit: Raquel Barrón MD@raquelbarron

Myofibroblasts



Slender tapered contours

DESMOPLASTIC FIBROMA (DESMOID TUMOR OF BONE)

MORPHOLOGY

- Infiltrative fascicles of uniform myofibroblasts with tapering nuclei

OTHER HIGH YIELD POINTS

- Rare, **young patients**, locally aggressive **benign** mandible tumor
- It may be related to trauma associated with **Gardner Syndrome**
- **IHC:** SMA+, nuclear Beta-catenin
- **Molecular:** *CTNNB1* hotspot mutations or *APC* gene (Autosomal Dominant)

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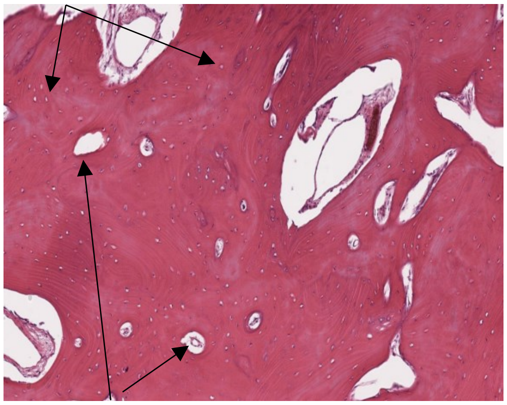
Cortical bone



Haversian-like canals

OSTEOMA

MORPHOLOGY

- Lamellar/cortical-type bone with inconspicuous osteoblasts
- Trabecular arrangement and Haversian-like canals

OTHER HIGH YIELD POINTS

- **Benign**, incidental finding usually on face or jaw
- Common incidental finding on imaging
- When develops in medullary cavity → "Bone Island."
- **Multiple osteomas** → think about **Gardner's Syndrome**

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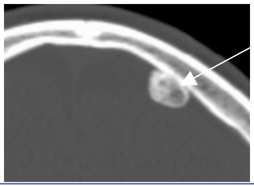
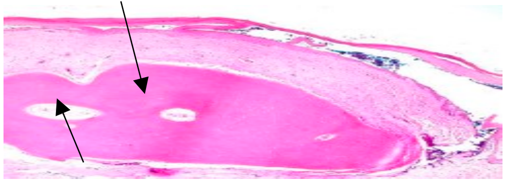


Osteoma


Dense lamellar bone
Fatty marrow

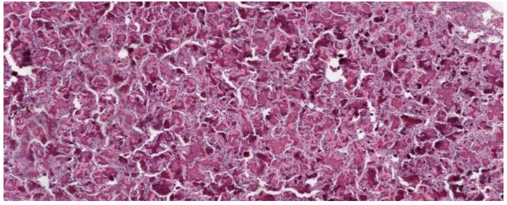
TORUS (EXOSTOSIS)

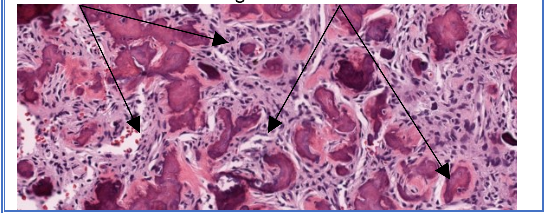
MORPHOLOGY

- Usually composed of **dense, mature, lamellar bone**
- **Minimal** osteoblastic **activity** and **fatty marrow**

OTHER HIGH YIELD POINTS

- **Benign** and requires clinical since it is identical to osteoma
- **Three main locations:** Palate, Mandible, and Buccal


Irregular, curvilinear woven bone


Fibrous tissue
Irregular woven bone

FIBROUS DYSPLASIA (FD)

MORPHOLOGY

- Proliferation of irregular, **curvilinear woven bone** with **inconspicuous osteoblastic rimming**
- **Fibrous tissue** is composed of **bland fibroblastic cells**

OTHER HIGH YIELD POINTS

- **Benign** can be mono or polyostotic; **monostotic more common**
- **Failure** to **form mature lamellar** bone
- **Found in first three decades, M=F,** syndromic associations
- **McCune-Albright**: FD, >3 café-au lait spots, endocrine abnormalities
- **Mazabraud Syndrome**: Females > Males, soft tissue myxomas + FD
- **Mutation:** De Novo *GNAS* mutations

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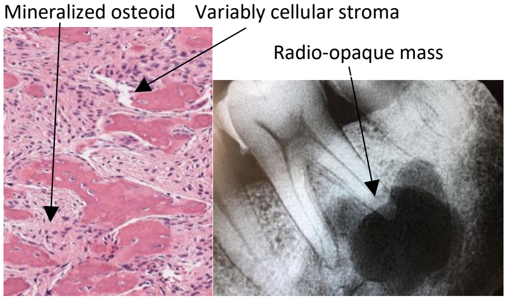
Mineralized osteoid
Variably cellular stroma
Radio-opaque mass

Radiographic image by: Kaisen Yao, MD

CEMENTO-OSSEOUS DYSPLASIA

MORPHOLOGY

- Mineralized osteoid and cementum-like material, variably cellular fibrous stroma

OTHER HIGH YIELD POINTS

- **Benign** occurs exclusively in tooth-bearing regions of jaws
- **Common,** especially in Black females
- **Radiology** shows **radiopaque structures**

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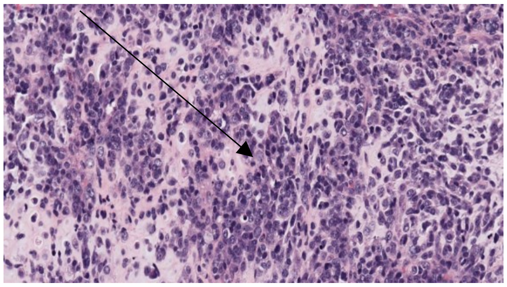
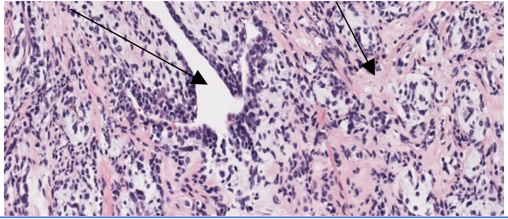

Small round cell


Staghorn vessel
Hyaline cartilage

MESENCHYMAL CHONDROSARCOMA

MORPHOLOGY

- Biphasic tumor with Islands of **organized** hyaline cartilage nodules
- Undifferentiated small round cell component with high nuclear to cytoplasm ratio
- Frequent "**staghorn**" vessels
- Mitosis and necrosis

OTHER HIGH YIELD POINTS

- **Malignant** and **aggressive,** variable survival
- **Jaw** accounts for ~50% of sites
- **CT imaging:** Destructive lytic lobulated lesion with granular rings and arcs +/- calcification
- **IHC:** small round cell (CD99+, NKX2.2+ (~80%), +/- NKX3.1); cartilage S100+; all components SOX9+
- **Molecular: *HEY1-NCOA2* fusions → t(8;8)(q13;q21)**

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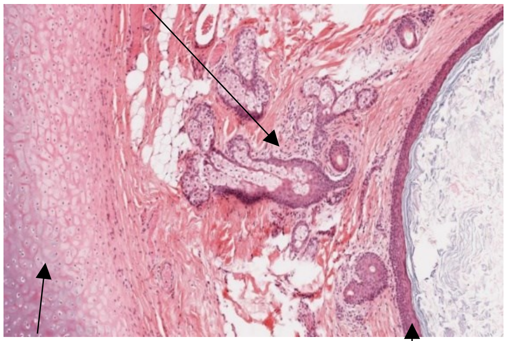
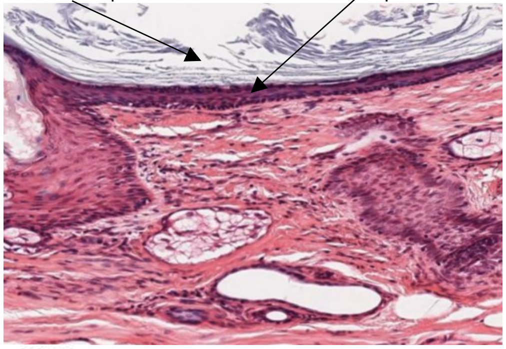
12. HEAD AND NECK PATHOLOGY





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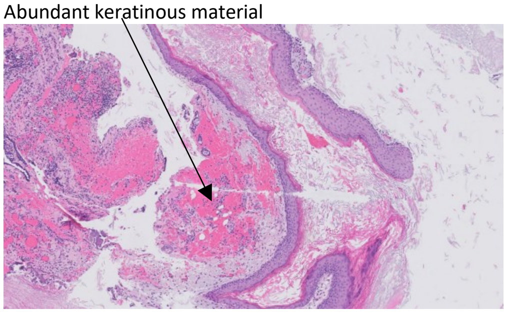
FIRST BRANCHIAL CLEFT ANOMALY (CYST)

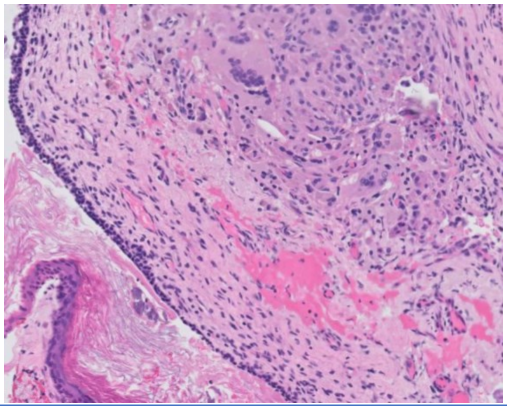
MORPHOLOGY

- **Cyst**, **fistula**, or a **sinus** that is lined by **stratified squamous epithelium** or **ciliated respiratory epithelium**
- Cyst will contain **sloughed anucleate squamous cells**
- **Cartilage** may be **present**
- May have associated **inflammatory response** (lymphoid aggregates) or due to secondary infection
- **Epithelium can be denuded** or replaced by granulation tissue

OTHER HIGH YIELD POINTS

- Due to **incomplete fusion of first and second branchial arches** which gives rise to the **persistent first branchial apparatus**
- Rare **syndromic association** with **Melnick-Fraser** syndrome or **congenital cholesteatoma**
- Can be **classified based on embryology & histology** (Work system):
  - **Type I:** composed of ectodermal elements only
    - **Epithelium only** without adnexal structures
    - **Most often is a cyst** rather than a fistula or sinus
  - **Type II:** composed of ectodermal and mesodermal elements
    - **Epithelium with adnexal structures** and may have cartilage
    - More common to have **associated sinus or fistula**
    - Discharge can be seen at skin surface
    - May **split cranial nerve VII**
- Most common in **children under 10** years old; 2:1 **female predominance**
- Presents as a **pre-auricular** or **post-auricular mass** that is soft and compressible with or without discharge
- **Treatment is surgical** and **may damage facial nerve** (CN VII) and it should be monitored during surgery





CHOLESTEATOMA

MORPHOLOGY

- Composed of **three main components**:
  - **Keratinizing stratified squamous epithelium** with a prominent granular cell layer and lacks rete ridges
  - **Anucleate** squamous **debris**
  - **Inflamed stroma** with variable granulomatous reaction

OTHER HIGH YIELD POINTS

- Clinically **aggressive** and may present as **conductive hearing loss**, **chronic** and **foul smelling otorrhea**, otalgia, and or headaches
  - **Conductive hearing** loss is **due** to **ossicular chain destruction**
  - If **vestibular symptoms** (vertigo, emesis, etc.) the **facial nerve** is **involved** and is most likely a petrous bone cholesteatoma which originates above the semicircular canals
- Associated as a long-term sequelae of chronic otitis media
- **Congenital cholesteatoma** arises from **epidermoid formation** and occur **behind** tympanic **membrane**
- **Acquired cholesteatoma** arise from **tympanic membrane perforations**
- **On imaging**, the lesion **can resemble a neoplasm** due to the destructive invasion into the drum/mastoid
- **Treatment is excision** but lesion can recur (20% of cases)

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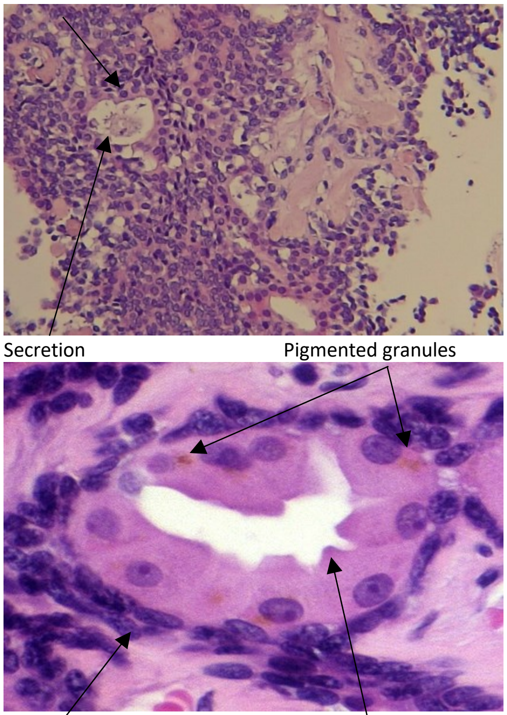

Image by Dr. Lester D.R. Thompson, MD, on Wikimedia

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CERUMINOUS ADENOMA

MORPHOLOGY

- **Ductal cells** have **luminal decapitation** and have **round nuclei** with conspicuous **small nucleoli**, **regular chromatin** distribution, and abundant **granular eosinophilic cytoplasm**
- Ductal cells may have **lipofuscin** or other **pigmented granules** from ceruminous debris
- Outer **myoepithelial cells** are organized **along basement membrane**
- Lesion is **unencapsulated** but is **well-circumscribed** with **dense fibrotic stroma**
- Variants have a **cystic** or **glandular pattern**
- Can be **moderately cellular** but has **minimal pleomorphism**, **mitotic activity**, and **lacks necrosis**

OTHER HIGH YIELD POINTS

- **Rare** neoplasm that is unique to **external auditory canal**
- There is **no sex predilection** and is seen in a **wide age range**
- Patients may **present with tinnitus**, **mixed** conductive and sensorineural **hearing loss**, otalgia, or may be asymptomatic
- **Treatment** is **surgical excision** which is often curative
- **Variants** of ceruminous adenoma include:
  - ➢ **Ceruminous pleomorphic adenoma** – had a chondromyxoid matrix and epithelial components
  - ➢ **Ceruminous papillary cystadenoma papilliferum** – has intraluminal papillae that are lined by cuboidal to columnar epithelium and have a dense plasma cell infiltrate
- **Immunohistochemistry:** useful to determine biphasic elements
  - ➢ **Ductal epithelial cells**: positive for cytokeratin, EM, and CK7; negative for neuroendocrine markers, CK20, and SATB2
  - ➢ **Basal cells**: positive for EMA, CK5/6, p40, p63, S100, SOX10, and CD117

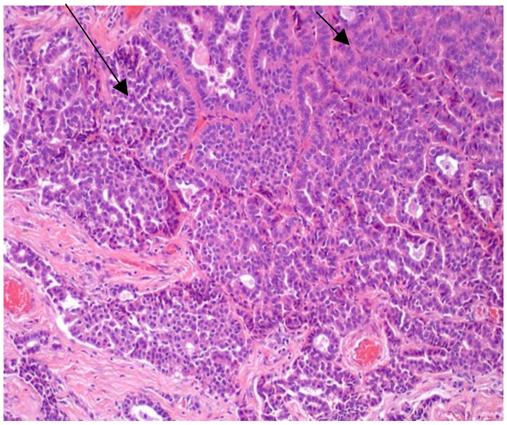
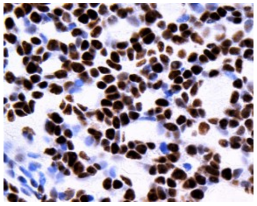
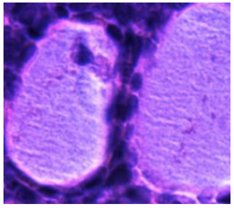


Image by Dr. Lester D.R. Thompson, MD on Wikimedia



IHC: CK AE1/AE3



Secretory material

MIDDLE EAR NEUROENDOCRINE TUMOR (MIDDLE EAR ADENOMA)

MORPHOLOGY

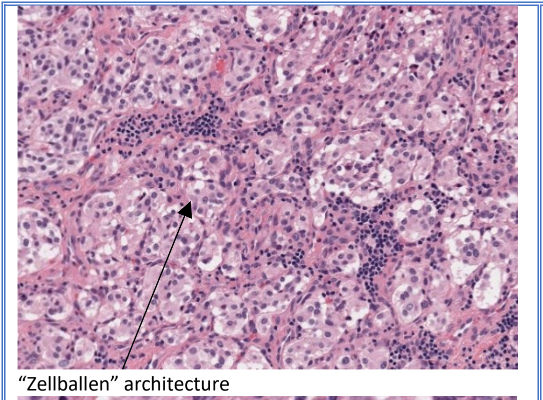
- Composed of **cuboidal** to **columnar epithelial cells** with round to **ovoid nuclei**, delicate **salt and pepper chromatin** pattern, and **variable eosinophilic cytoplasm**
- Can be arranged in **cords**, **trabeculae**, **glands** or **duct-like structures**, or single isolated cells
- Glandular or duct-like structures **may have secretions**
- No epithelial cells surround the epithelial cells

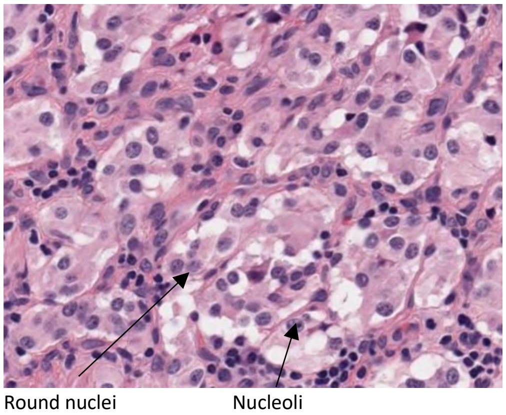
OTHER HIGH YIELD POINTS

- Presents as **unilateral**, conductive **hearing loss**, tinnitus, or ear pressure in **middle-aged adults**
- Previously called middle ear adenoma, but has been renamed
- Cellular with **infiltrative** growth; can involve bony ossicular chain
- **Lesion is nonfunctional** and there is **no secretion of hormones**
  - ➢ No utility for serum studies
- Low chance for recurrence; **complete surgical excision** usually **curative**
- IHC: Positive for pankeratin, CK5/6, CK7, INSM1, synaptophysin, chromogranin, SATB2

Path Presenter

JUGULOTYMPANIC PARAGANGLIOMA





MORPHOLOGY

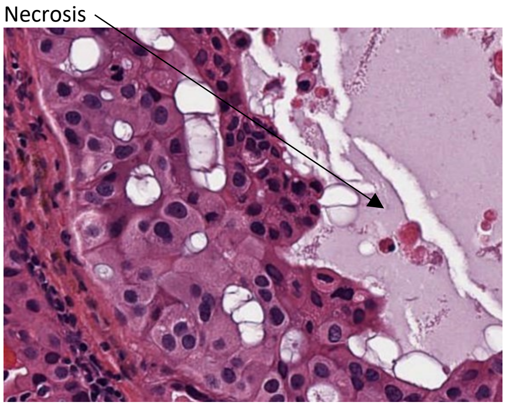
- **Non-epithelial neuroendocrine neoplasm** that is composed of small to intermediate sized **epithelioid cells** that have **round to ovoid nuclei**, **coarse** or **delicate chromatin**, and **abundant granular** basophilic **cytoplasm**
- The tumor cells are arranged in clusters or **Zellballen pattern**
- Background stroma is **rich in capillaries** and **occasional fibrosis**
- There may be scattered foci of **degenerative changes** from embolic event that lead to cystic change, hemorrhage, and hemosiderin deposition
- Edges are **often infiltrative** or **poorly circumscribed**

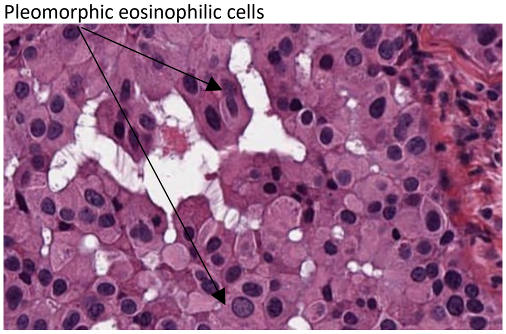
OTHER HIGH YIELD POINTS

- This is the **most common middle ear tumor** and has a **bimodal distribution**
  - ➢ **Familial lesions** are most often seen in the 3rd decade and affect males more than females
  - ➢ **Sporadic lesions** are seen in the 6th decade with significant female predominance
- All patients should receive **genetic testing** for VHL, SDH, RET, and NF1 mutations and genetic counseling
- **Prognosis is excellent** and only is associated with a ~15% mortality that is related to adjacent vital structure damage
- **Loss of SDHB** is associated with an increased risk of metastasis
- **Immunohistochemistry:** Positive for **S100 protein** (**sustentacular** cells), INSM1, synaptophysin, chromogranin; familial associated lesions show loss of **SDHB**

Path Presenter

CERUMINOUS ADENOCARCINOMA





MORPHOLOGY

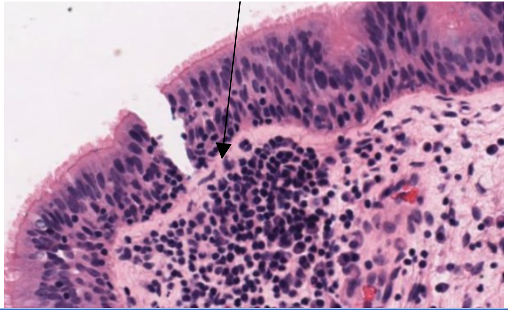
- **Biphasic malignant neoplasm** composed **epithelial cells** and **basal cells**
- **Epithelial cells** that have nuclear **pleomorphism**, **prominent** and conspicuous **nucleoli**, and **eosinophilic cytoplasm**
- Frequently has **comedonecrosis**, perineural invasion, scattered mitoses
- Arranged in **various patterns** such as solid, cribriform, cystic, glandular
- **No cerumen** is present in the lesion
- **Subtypes include:** Ceruminous adenoid cystic carcinoma (CACC) and Ceruminous mucoepidermoid carcinoma (CMEC)

OTHER HIGH YIELD POINTS

- **Very rare neoplasm** with a slight middle-aged female predominance
- Patients present most commonly with **otalgia**, followed by **tinnitus**, conductive and sensorineural hearing loss
- Auditory examination will demonstrate a **polypoid mass** towards the posterior aspect of the external auditory canal
- **Recurrence is common** (50% of all cases) and 50% die within 5 years
- Immunohistochemistry:
  - ➢ **Epithelial cells:** Positive for CD117 and CK7
  - ➢ **Basal cells:** Positive for CK5/6, p63, p40, and s100
- Must **rule out metastatic disease** or **direct extension** from **parotid primary** adenocarcinoma

Path Presenter

12. HEAD AND NECK PATHOLOGY



RHINOSINUSITIS

MORPHOLOGY

- **Mixed acute or lymphoplasmacytic infiltrate with background edema**
- Surface squamous metaplasia or reactive changes
- Chronic rhinosinusitis often associated with inflammatory polyps

OTHER HIGH YIELD POINTS

- **Inflammatory lesion**, **involving** either **nasal cavity** or paranasal **sinuses**
- Wide age range and equal sex distribution
- Most common cause is **allergies**, other causes include **anaerobic bacterial overgrowth** from obstruction

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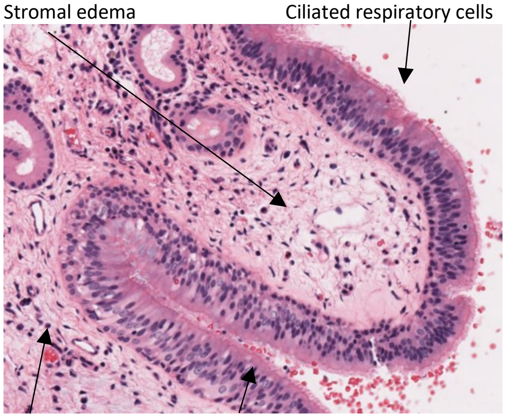


Path presenter

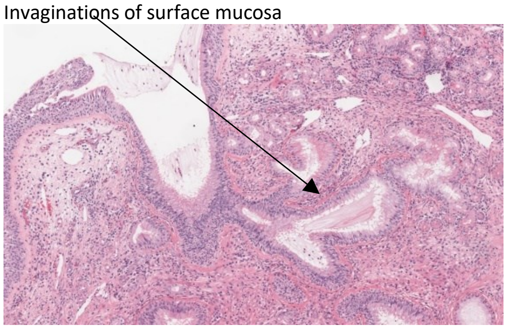
SINONASAL INFLAMMATORY POLYPS

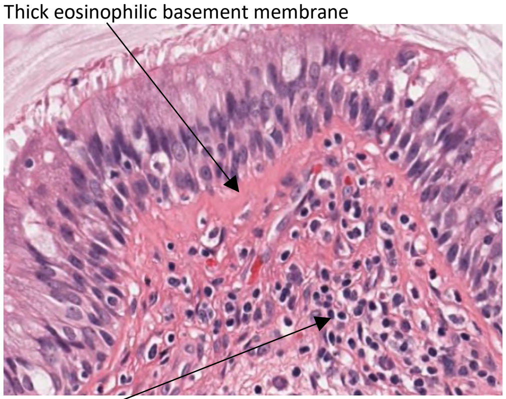
MORPHOLOGY

- Benign **ciliated respiratory epithelium** lines the surface of the polyp
- Underlying **stroma is edematous** and has a **mixed chronic inflammatory** infiltrate composed of eosinophils, lymphocytes, and plasma cells
- **Vessels** may be an **ectatic** within the lesion
- **Secondary changes** may include **squamous metaplasia**, **ulceration**, **fibrosis**, infarction, **granulation tissue**, **amyloid-like** deposition within the stroma, and osseous or collagenous metaplasia
- **No seromucinous glands** are present

OTHER HIGH YIELD POINTS

- Seen most often in association with **allergic rhinosinusitis**
- Usually **seen in adults** with rhinorrhea, nasal obstruction, or headaches
- Polyps originate from the **lateral nasal wall** or **ethmoid recess**
- Despite surgical management, nearly 50% of all patients will have recurrence; **recurrence is higher in those** with **aspirin intolerance** or **asthma**




Thick eosinophilic basement membrane
Chronic inflammatory cells

RESPIRATORY EPITHELIOID ADENOMATOID HAMARTOMA (REAH)

MORPHOLOGY

- **Invaginated sinonasal glandular proliferation** arising from surface epithelium
- **Small to medium-sized glands** with **hyalinized intervening stroma** with a peripheral **thick eosinophilic basement membrane**
- The glands are **lined** by **respiratory epithelium**
- May have **squamous** or **osseous metaplasia**, and **hyperplasia**
- Stroma may contain a **mixed chronic inflammatory** cell **infiltrate**

OTHER HIGH YIELD POINTS

- Most common in **adults in the 6th decade**; no sex predilection
- Patients usually present with 1 or more symptoms that may include nasal stuffiness, obstruction, right sinusitis, or epistaxis
- Main treatment is **curative surgical resection**
- **Differential includes sinonasal hamartoma**
  - Sinonasal hamartoma is a submucosal proliferation of small glands or acini in tubules that grow in lobules or clusters that are arranged in a haphazard configuration
- **Immunohistochemistry**:
  - **Epithelium:** Positive for cytokeratin AE1/AE3, CAM 5.2, CK7; **negative** for **CDX2** and **CK20**
  - **Myoepithelial cells:** Positive for p63 and S100

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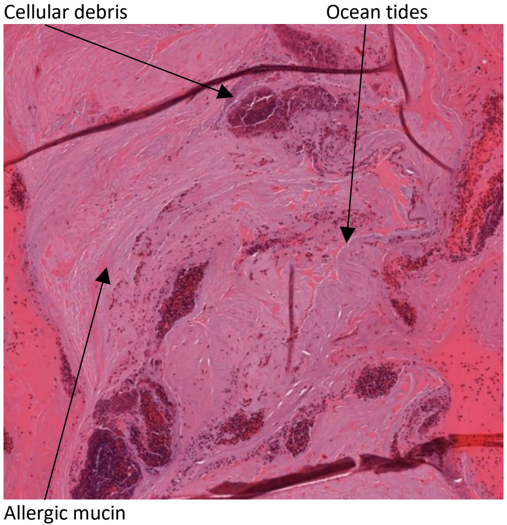
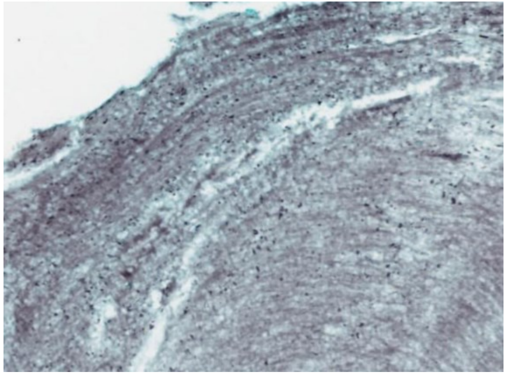
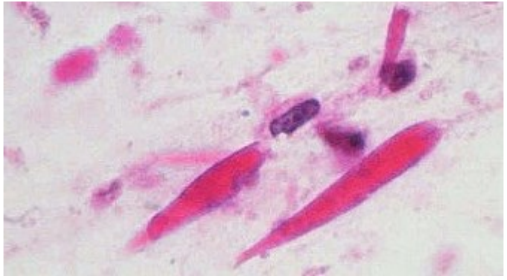




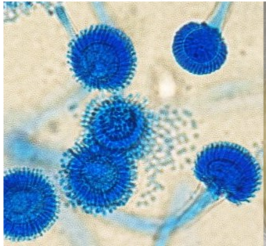
GMS Stain: Fungal hyphae

Charcot-Leyden Crystals



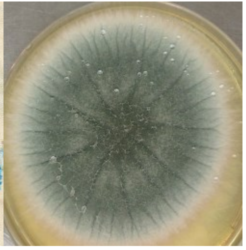
Courtesy of Dr. José Jiménez Heffernan on Wikimedia

Aspergillus fumigatus



By: A. Baggio on Wikimedia

A. fumigatus culture



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ALLERGIC FUNGAL SINUSITIS

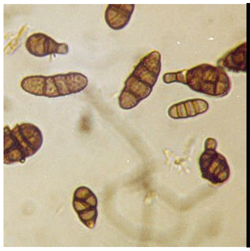
MORPHOLOGY

- **Allergic mucin**: lamellated mixture of inflammatory cells, Charcot-Leyden crystals, and mucin
- Mucinous material has a **wavy pattern** similar to "**ocean tides**" or "**waves**"
- The degenerating debris is from neutrophils and eosinophils
- **Charcot-Leyden Crystals:** Long dense **eosinophilic needle shaped** or bipyramidal crystals which are refractile
- **Fungal elements** may be present

OTHER HIGH YIELD POINTS

- **Most common fungal sinusitis** in **immunocompetent adults**
- More **common in** locations with **warmer climates**
- Patients usually complain of **chronic rhinorrhea**, **headaches**, or have a **nasal cavity mass** causing obstruction
- Most common in the **maxillary** and **ethmoid sinuses** or the **nasal cavity**
- The **pathogenesis is due to environmental exposure**
    - ➢ Inspired **fungal elements create an immune response** due to the antigen presenting cells using the MHC class II
    - ➢ The predominant immunoglobulin response is IgE (type 1 hypersensitivity reaction)
    - ➢ The most common organisms are **Aspergillus** or the **dematiaceous molds** ("**ABCEP**" → Alternaria, Bipolaris, Curvularia, Exserohilum, or Phialophora)
- Treatment includes a desensitization, surgery, and/or medications
- **Recurrence is common** and can cause reduced functional status of patient
- **Special stains:** Fungal elements may be seen on GMS or PAS

Alternaria



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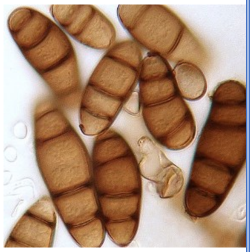
Alternaria culture

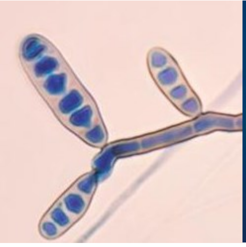
By: L. He on Wikimedia

Curvularia

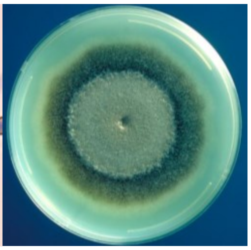


By: Medmyco on Wikimedia

Exserohilum

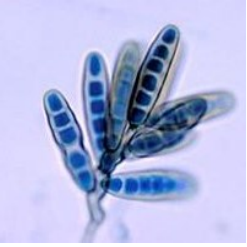


Exserohilum culture



Courtesy: Dr. Libero Ajello at CDC on Wikimedia

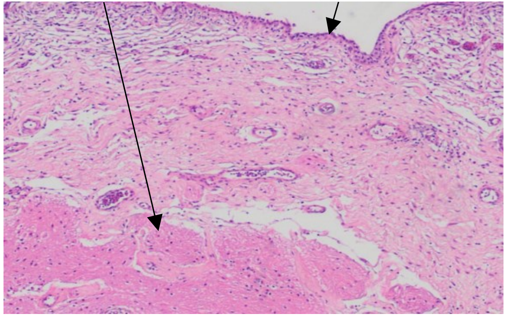
Bipolaris

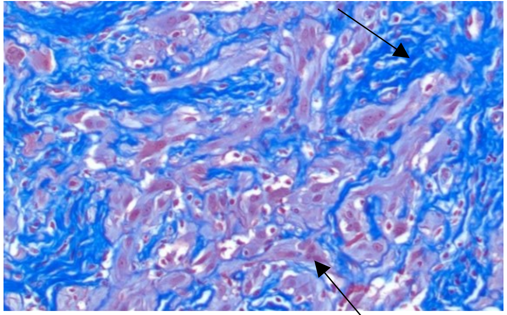


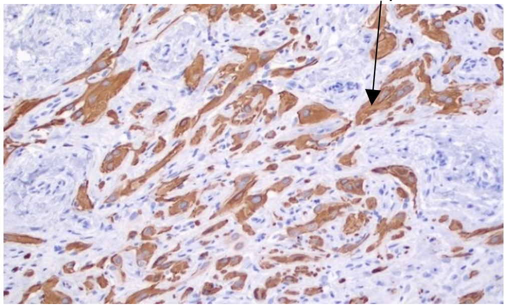
Courtesy: CDC on Wikimedia

[Path Presenter]

12. HEAD AND NECK PATHOLOGY







CT Scan, Trichrome, GFAP by: Soca1zim on Wikimedia

NASAL GLIAL HETEROTOPIA

MORPHOLOGY

- A **glial fibrillary network** is seen **within** the **sinonasal connective tissue**
- **Neuroglial** tissue can present in **nests or sheets** and **may have** few **gemistocytes**
- Although very rare, choroid plexus, ependymal, or retinal pigmented cells may be seen
- **Overlying epidermis** or **mucosal surface** is **undisrupted**
- **No presence of dura/leptomeninges/neurons**

OTHER HIGH YIELD POINTS

- Most **commonly is seen in infancy** with an **equal sex distribution**
- Thought to be **congenital defect** in which the **frontal lobe does not completely retract** into the **cranial cavity**
- Can be further classified into subtypes based on location
  - **Extranasal (Most common):** Lesion arises in the subcutaneous soft tissues of the nasal bridge and presents as a firm subcutaneous nodule
  - **Intranasal:** Lesion arises in the superior nasal cavity and presents as a polypoid mass that may cause obstruction
  - **Mixed (least common):** Both intranasal and extranasal
- Treatment includes **complete surgical excision**
- The **main differential is an encephalocele**, which will **show the presence of meninges** or neurons
- **Immunohistochemistry:** The glial cells are **positive for GFAP** and **S100**
- **Special stains: Trichrome stain** the **glial tissue will be red** whereas the **fibrotic collagen** will stain **blue**

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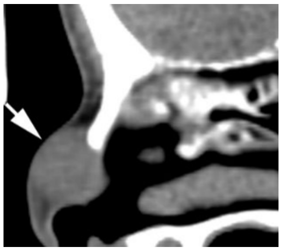
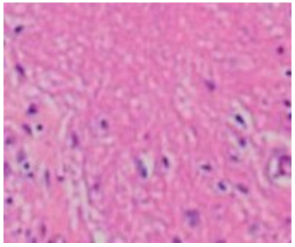
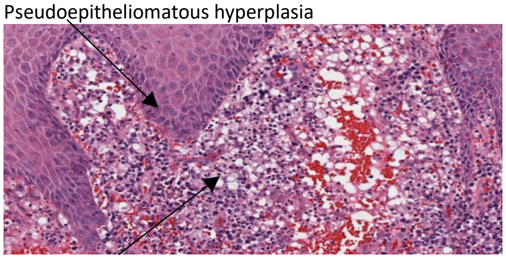
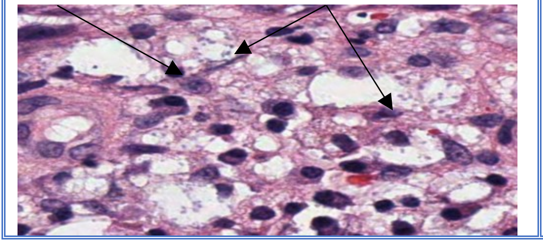
CT Scan



Fibrillary network







RHINOSCLEROMA

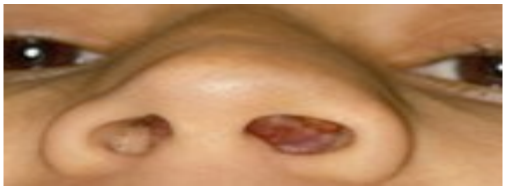
MORPHOLOGY

- **Expansile sheets** of **inflammatory** cells predominantly **plasma cells**
- The plasma cells may be **Mott cells** or have **Russell bodies**
- Increased **foamy histiocytes** (**Mikulicz cells**) which will be **filled with bacilli**
- Additional features may include **pseudoepitheliomatous hyperplasia**, **mucosal ulceration**, **submucosal cyst** containing keratin, or vasculitis

OTHER HIGH YIELD POINTS

- Most often seen in the 2nd 3rd decade of life with a female predominance
- Increased incidence within Egypt, India, Central America, or Eastern Europe
- Lesion progresses through different phases:
  - **Catarrhal** phase (rhinitic)
  - **Proliferative** phase (granulomatous)
  - **Cicatricial** phase (fibrosing)
- Causative pathogen is Klebsiella rhinoscleromatis
  - A non-motile, encapsulated, gram negative bacillus
  - Culture with a MacConkey agar
  - Susceptible to tetracyclines and fluoroquinolones

Rhinoscleroma in a child from South America

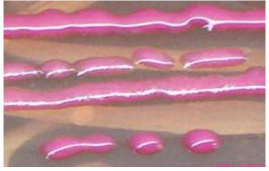


Provided by: Dr. Fred L. Herbert, MD on Wikimedia

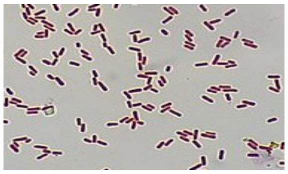
- Special stains: Warthin-Starry (silver stain) is the most sensitive

Path Presenter

MacConkey with Klebsiella

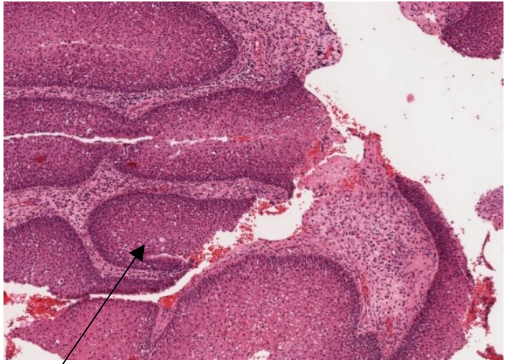


Gram stain of Klebsiella



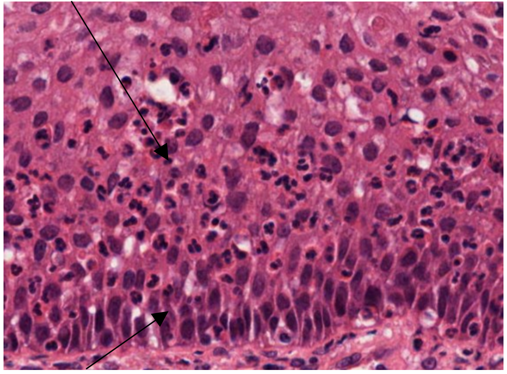
SINONASAL PAPILLOMA				
Type	**Morphology**	**Location**	**Risk of Malignant Transformation**	**Molecular Findings**
Exophytic	Exophytic growth, immature squamous epithelium	Nasal septum	Very low risk	Low-risk HPV subtypes
Inverted	Inverted ribbonlike growth, immature squamous epithelium, transmigrating intraepithelial neutrophilic inflammation	Lateral wall and sinuses	Low to intermediate risk	EGFR mutations, low-risk HPV subtypes
Oncocytic	Exophytic and endophytic growth; multilayered oncocytic epithelium, microcytes and intraepithelial neutrophilic microabscess	Lateral wall and sinuses	Low to intermediate	KRAS

Immature squamous epithelium



Inverted growth

Transmigraing neutrophils



Bland squamous cells

SINONASAL PAPILLOMA, CLASSIC INVERTED TYPE

MORPHOLOGY

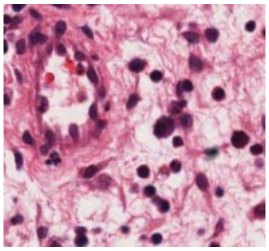
- **Inverted "ribbonlike" growth** with **immature squamous** epithelium
- **Bland squamous epithelium** with **uniform nuclei** with **mild pleomorphism** and have **clear to eosinophilic cytoplasm**
- **Mitotic figures** are usually **confined to the basal** and **parabasal layers** but lack atypical forms
- There may be **foci of transitional** or **columnar epithelial cells** and have mixed **goblet cells** or **mucus cysts** within the epithelium
- Variable amount of **transmigrating inflammatory** cells within the epithelium
- Underlying **stroma is variable** and may be fibrous, myxoid, or edematous
- **Variable vascularity** within the stroma

OTHER HIGH YIELD POINTS

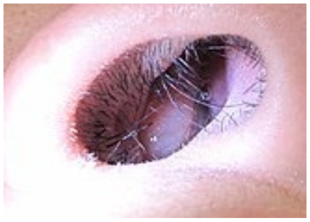
- Typically, in **middle-aged** to **elderly males** and in **lateral wall** or **sinuses**
- There is a **low to intermediate risk** for **malignant transformation**
- **Recurrence is common** in more than half of all cases
- **Immunohistochemistry**: May be positive for p16; KI-67 proliferation index is usually low and confined to the basal or parabasal layer
- **RNA in situ hybridization:** Positive for low-risk HPV6/11
- Molecular:
  - More than **90% of cases** will have a **somatic EGFR Exon 20 mutation**
  - if a **TP53 gene mutation** is present, **consider malignant transformation**

Path Presenter

Edematous Stroma

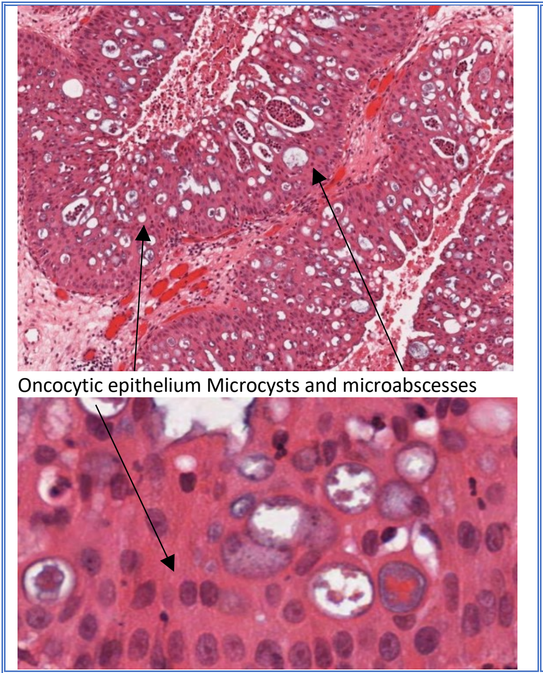


Nasal polyp on Examination



By: MathieuMD on Wikimedia

12. HEAD AND NECK PATHOLOGY



SINONASAL PAPILLOMA, ONCOCYTIC TYPE

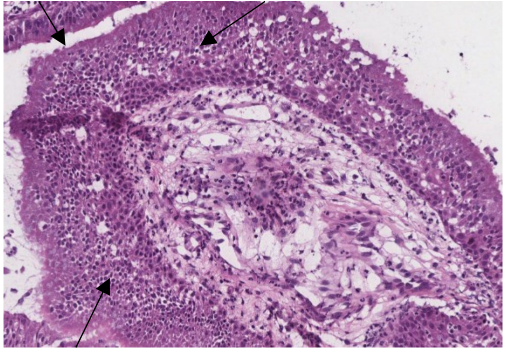
MORPHOLOGY

- **Multilayered proliferation** of **oncocytic cells** with nuclei that have vesicular or **hyperchromatic chromatin**, **inconspicuous nucleoli**, and have abundant **granular**, **eosinophilic cytoplasm**
- The proliferation is arranged as an **exophytic or endophytic growth** pattern
- Has scattered **intraepithelial cysts** containing **neutrophilic microabscesses**
- Variably **fibrous or myxoid stroma**, **variable inflammation** and **vascularity**
- The **nuclei** of the basal and luminal cells exhibit "**tram track**" **formation**

OTHER HIGH YIELD POINTS

- Usually seen in **middle aged to elderly adults** and has **equal sex distribution**
- Most common location is **lateral nasal wall,** or the **maxillary**, **ethmoid**, or **paranasal sinuses**
- The **risk of malignant transformation** is **up to 10%,** of which the most common malignancy is a **keratinizing squamous cell carcinoma**
- **Immunohistochemistry:** May be positive for p16; KI-67 proliferation index is usually low and confined to the basal or parabasal layer
- **RNA in situ hybridization:** Positive for low-risk HPV6/11
- **Molecular:** Activating KRAS mutations

Path Presenter



Path Presenter

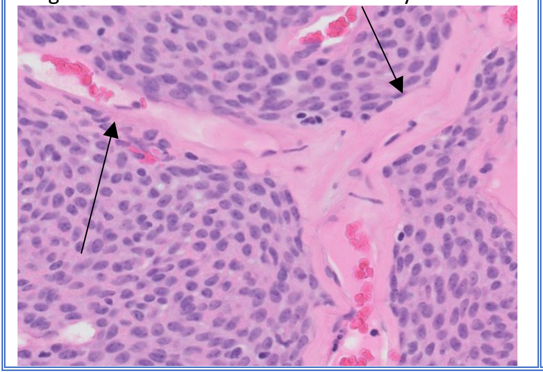
SINONASAL PAPILLOMA, EXOPHYTIC TYPE

MORPHOLOGY

- **Exophytic proliferation** of **thickened squamous epithelium** that have **nuclei** that **are crenated** ("raisinoid"), a **perinuclear halo**, and conspicuous cellular borders (koilocytic change)
- **Papillary fronds** may be lined by respiratory epithelium but is less common
- There are scattered **goblet cells** and **intraepithelial mucous cysts**
- Surface **keratinization** is **uncommon**

OTHER HIGH YIELD POINTS

- **Predominantly** seen in **males** (10:1) in the **3rd-5th decade** of life
- Largely involves only the **lower anterior portion of the nasal septum**
- **Extremely low risk for malignant transformation** (<1%)
- Associated with **low-risk HPV subtypes**
- **Immunohistochemistry:** May be positive for p16; KI-67 proliferation index is usually low and confined to the basal or parabasal layer
- **RNA in situ hybridization:** Positive for low-risk HPV subtypes
- **Molecular: Lacks EGFR and KRAS mutations** that are seen in other subtypes



GLOMANGIOPERICYTOMA

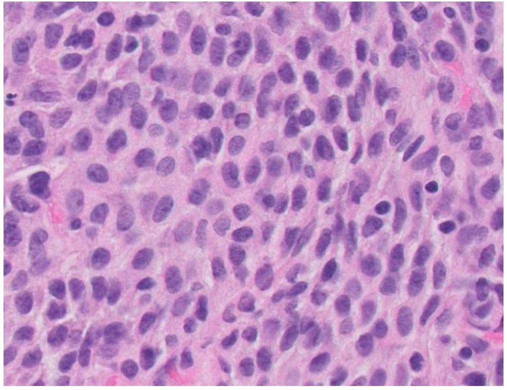
MORPHOLOGY

- The **surface is covered** by **benign respiratory epithelium** or metaplastic squamous epithelium
- A space clearing (**Grenz zone**) between the surface epithelium and stroma
- The submucosa contains a "**patternless" pattern of spindled to epithelioid cells** that have **ovoid nuclei**, **coarse chromatin**, and **amphophilic** to **eosinophilic cytoplasm without distinct borders**
- The **spindled cells** may have a **diffuse cellular** or **syncytial arrangement**
- Vessels are **staghorn-like configuration** with **perivascular hyalinization**
- **Extravasated erythrocytes**, **eosinophils** and **mast cells** are **present**

OTHER HIGH YIELD POINTS

- **Rare sinonasal neoplasm** seen in **elderly** with **slight female predominance**

Spindled to epithelioid cells



- Presents as an **obstructing mass**, difficulty breathing, or rhinorrhea
- Rarely **associated** with **oncogenic osteomalacia**:
  - Will have increased alkaline phosphatase, hypophosphatemia, and a normal PTH and calcium level in the serum
- **Excellent prognosis** that has a 90% survival at 5-years and recurrence in 33% of cases that have bone invasion or nuclear pleomorphism
- **Immunohistochemistry:** Positive for nuclear β-catenin, LEF1, SMA (and other actins), cyclin D1 (nuclear); negative for CD31, CD34, and Factor VIIIR antigen
- **Molecular: Single nucleotide substitutions** in **exon 3** of **CTNNB1**
  - Consequence is constitutively active β-catenin and will have aberrant accumulation within the cell nucleus

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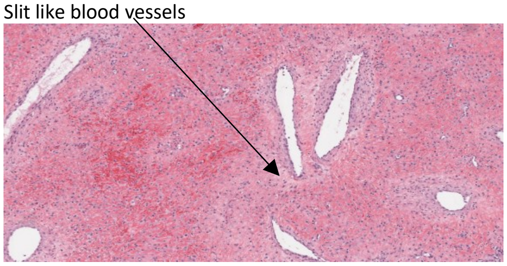
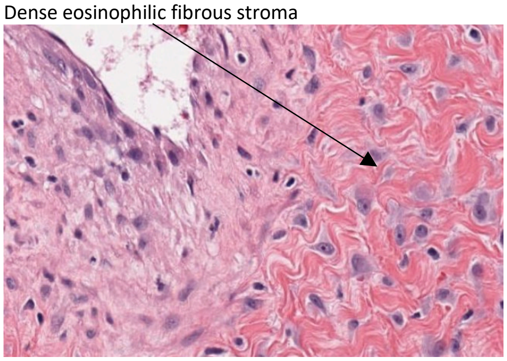
Slit like blood vessels



Dense eosinophilic fibrous stroma



NASOPHARYNGEAL ANGIOFIBROMA

MORPHOLOGY

- **Rich vascular tumor** with **variably sized slit-like blood vessels**
- **Fibrocollagenous** stromal **background**
- **Vessels** can be **small and delicate capillaries or** be **ectactic** and have attenuated or plump endothelial cells
- Stroma can **develop myxoid degeneration from embolization** procedure
- **Mast cells** are frequently **seen** throughout
- **Rare mitotic figures** may be identified

OTHER HIGH YIELD POINTS

- **Rare benign lesion** that is most common in **young** to **adolescent males**
- Patients present with **chronic recurrent epistaxis**, obstruction, diplopia, tinnitus or deafness, and headaches
- Associated with **FAP syndrome**
- Most commonly is **seen in the posterolateral nasopharynx**
- **Good prognosis** from surgical management but **recurrence** is seen usually in the **first two years** and occurs **in nearly 25% of cases**
- **Immunohistochemistry:** Stromal cells are **positive for AR** and **β-catenin** (nuclear); negative for desmin, SMA, and CD34

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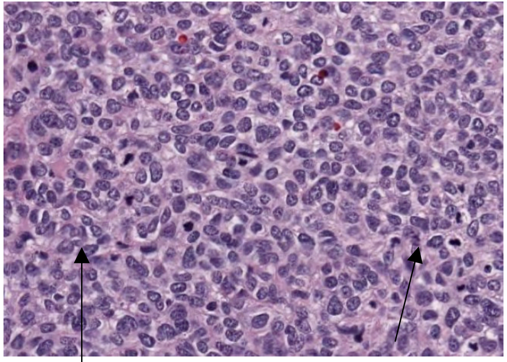
Malignant squamous cells



Nuclear pleomorphism

Hyperchromatic

Path Presenter

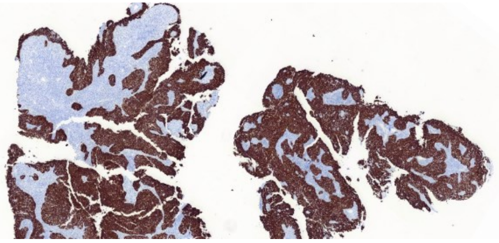
SQUAMOUS CELL CARCINOMA

MORPHOLOGY

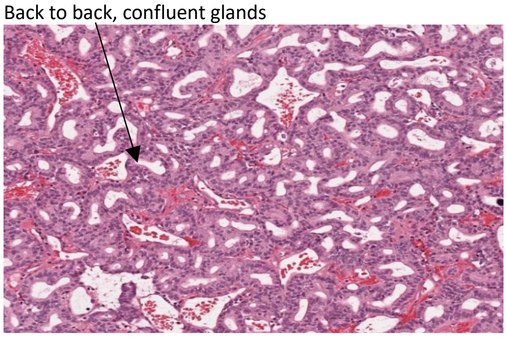
- **Malignant proliferation of squamous cells** with variable cytologic features
- **Keratinizing subtype** has enlarged polygonal cells with nuclear pleomorphism, and cytoplasm that demonstrates intracellular bridges to adjacent cells
- **Nonkeratinizing subtype** has hyperchromatic cells with an increased nuclear to cytoplasm ratio, irregular nuclear contours, nuclear pleomorphism, and little cytoplasm
- Additional **subtypes** include **basaloid, papillary, adenosquamous, spindled, acantholytic**

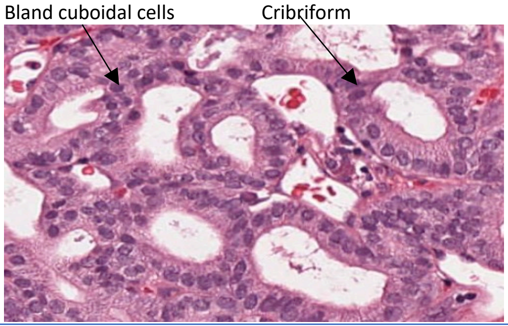
OTHER HIGH YIELD POINTS

- **Most common malignant epithelial tumor of the sinonasal tract** and approximately **10% are bilateral lesions**
- Usually is seen in **elderly males** in the **6th and 7th decade**
- Most common site is the **antrum of maxillary sinus**, or nasal cavity


IHC:CK5/6

- **Keratinizing subtype accounts for 60% of cases** and
- **Survival is fair** and ranges from 45% to 65% (5-year)
- **Immunohistochemistry:** positive for p40, p63, CK5/6, CKAE1/AE3
    - Nonkeratinizing type: block positive for p16, may have neuroendocrine marker reactivity, intact SMARCA4 (BRG1) and SMARCB1 (INI1)
- **RNA in situ hybridization:** Positive for high-risk HPV subtypes
- **Molecular:**
    - Mutations in TP53, EGFR, PTEN, CDKN2A, or KMT2D
    - RNA fusions of DEK::AFF2 seen in HPV negative (mutually exclusive)
    - DEK::AFF2 associated with increased recurrence rate


Back to back, confluent glands


Bland cuboidal cells

Cribriform

SINONASAL ADENOCARCINOMA, NON-INTESTINAL TYPE

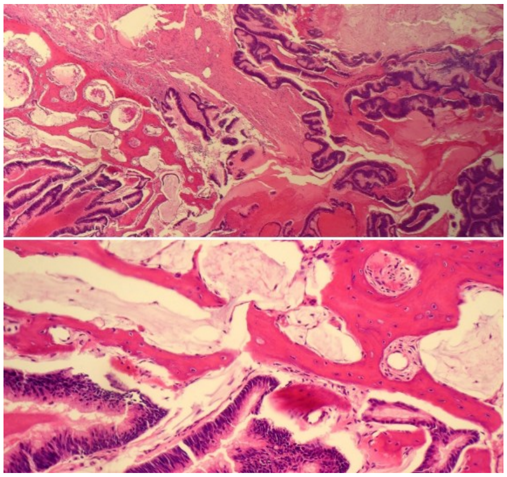
MORPHOLOGY

- **Low Grade: Monotonous bland cuboidal** cells with round, **basally located nuclei,** eosinophilic cytoplasm, and is **arranged in a cribriform pattern**
- **High Grade:** Epithelial cells with **pleomorphic nuclei**, **prominent nucleoli**, **variable chromatin** pattern, **eosinophilic cytoplasm**, and **frequent mitoses** and **apoptosis**
    - Has a destructive growth pattern and invasion into nerves, vessels, lymphatics, and adjacent structures

OTHER HIGH YIELD POINTS

- Typically seen in **elderly males** in the **6th decade,** and has **no association** with **predisposing exposure**
- **Low grade is most common** in the **ethmoid** sinus, with **equal sex** distribution
    - **Prognosis is excellent** at 5-years with a 70% survival and recurrence common in 25% of patients but rarely metastasizes
- **High grade** is most common in **maxillary sinus**, **male predominance**
    - **Poor prognosis** with only 20% survival at 3-years and 33% have distant metastasis
- **IHC: positive** for **CK7**, S100; **negative** for **CK20**, **CDX2**, and **villin**

Path Presenter


Courtesy: Dr. Anne Mills

Path Presenter

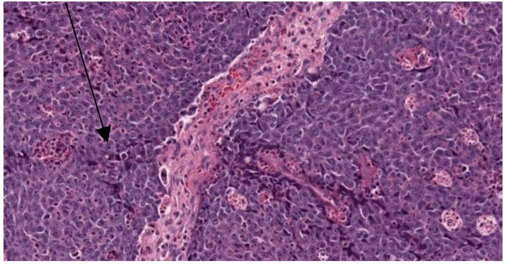
SINONASAL ADENOCARCINOMA, INTESTINAL TYPE

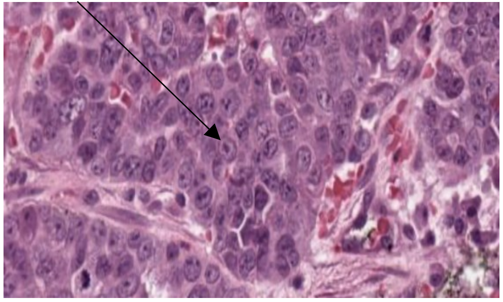
MORPHOLOGY

- Malignant epithelial cells that have variety of morphology and configurations
- **Colonic subtype (Most common):** Cells with increased nuclear pleomorphism and is arranged in a tubuloglandular architecture with central "dirty" necrosis
- **Papillary subtype:** Cells with little cytologic atypia and are arranged in papillary fronds and have few tubular glands
- **Solid subtype:** Cells show loss of differentiation, increased pleomorphism, vesicular nuclei, conspicuous nucleoli, and increased mitotic activity
- **Mucinous subtype:** Can be solid, glandular, signet-ring, or papillary fronds

OTHER HIGH YIELD POINTS

- Most common in **adults in the 5th decade** of life
- The most common location is the **ethmoid sinus** followed by nasal cavity
- Approximately **10% of patients have bilateral disease**
- Males usually have environmental exposure to **wood/leather dust** particulate
- **Locally aggressive cancer** with a **60% 5-year survival** and **high recurrence rate**
- **Metastasis** is only seen in **about 10% of cases**
- IHC: positive for intestinal markers (CDX2, CK20, villin), MUC2, MUC4





SINONASAL UNDIFFERENTIATED CARCINOMA (SNUC)

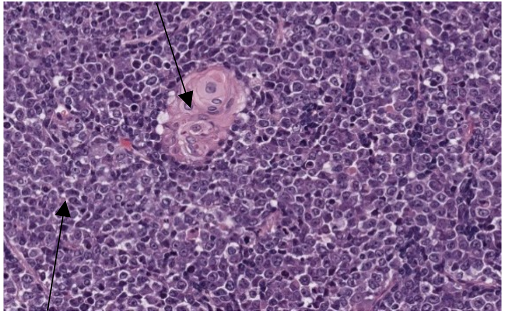
MORPHOLOGY

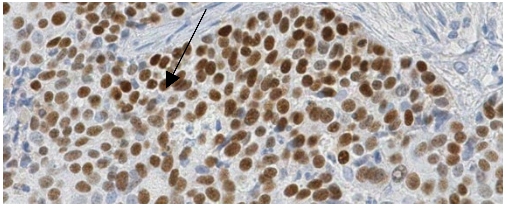
- **Monotonous polygonal epithelial cells** with **oval vesicular** to **hyperchromatic nuclei**, inconspicuous to conspicuous eosinophilic **nucleoli**, and **eosinophilic** cytoplasm and **poorly defined borders**
- Malignant cells are **arranged in various patterns**: solid, trabecular, sheets, organoid, lobular, or ribbon-like
- **Necrosis** and abundant **mitotic activity** are **common**
- **Lymphovascular** and **perineural invasion** are **common**

OTHER HIGH YIELD POINTS

- **Rare carcinoma** that has a **male predominance** with wide age distribution
- Has **rapid onset of nasal symptoms**, visual disturbance, and pain
- Lesion has **aggressive growth** and occurs within multiple contiguous sites
- **Poorly differentiated carcinoma without** squamous, glandular, or neuroendocrine differentiation → diagnosis of exclusion
- **Aggressive high-grade malignancy** with poor outcomes
- IHC: positive for cytokeratin, **negative for squamous markers**
- **Molecular:** IDH2 R172 mutations are seen in most cases

Path Presenter





NUCLEAR PROTEIN IN TESTIS (NUT) CARCINOMA

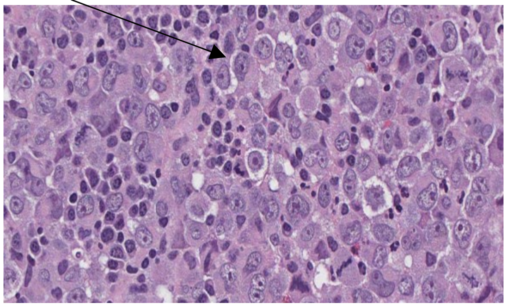
MORPHOLOGY

- **Primitive cells with round nuclei** and **amphophilic cytoplasm** with "**abrupt**" **keratinization** or **squamous differentiation**
- Tumor cells are arranged in **expansile sheets**
- Brisk **mitotic activity** is seen **throughout**
- **Necrosis**, **inflammation**, **lymphovascular,** & **perineural invasion** are common

OTHER HIGH YIELD POINTS

- **Poorly differentiated carcinoma**
- Typically, **younger patients** with **midline head/neck, mediastinal lesions**, but not exclusive to this region or midline
- **Rapid onset** and nearly **50% of cases have metastasis** at **diagnosis**
- **Very poor survival**, median survival is **<1 year**
- **IHC**: **Positive for NUT** (speckled nuclear positivity), CK5/6, p40, p63 cytokeratin, CD34 (variable)
- **Molecular**: **BRD4::NUTM1 fusions** →t(15;19) or BRD4::NUTM1-variant

Path Presenter



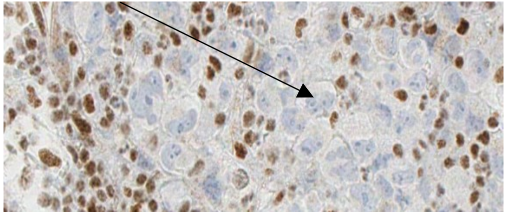
SWI/SNF COMPLEX DEFICIENT SINONASAL CARCINOMA (SMARCB1-DEFICIENT)

MORPHOLOGY

- **Monotonous polygonal epithelial cells** with **eccentric nuclei** that have variable chromatin, **conspicuous nucleoli**, and **eosinophilic cytoplasm** and **poorly defined borders**
- May have **prominent basaloid** or **plasmacytoid** to **rhabdoid features**
- Tumor cells are arranged in nests, sheets, cords, and/or lobules
- **Lacks frank keratinization** and squamous differentiation

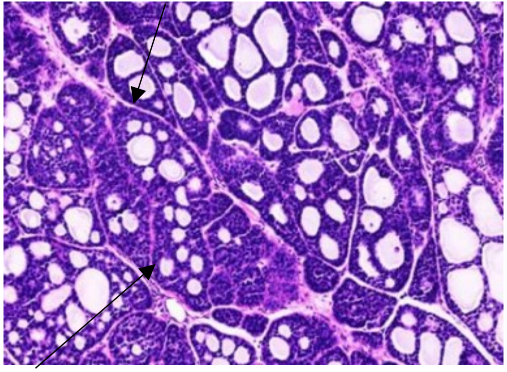
OTHER HIGH YIELD POINTS

- **Rare carcinoma** that has a **slight male predominance** and typically occurs in the 5th decade


Loss of INI-1 staining

- The most **common location** is the **nasal ethmoid region**
- **Nearly all cases are pT4 at time of diagnosis** and have a **poor prognosis**
- **Immunohistochemistry**: **Loss of INI1** by IHC
- **Molecular**: **Homozygous** (most common) or **heterozygous deletion** of **SMARCB1** (INI1)

Path Presenter


Mimic of adenoid cystic carcinoma

Basaloid cells

HPV-RELATED MULTIPHENOTYPIC CARCINOMA

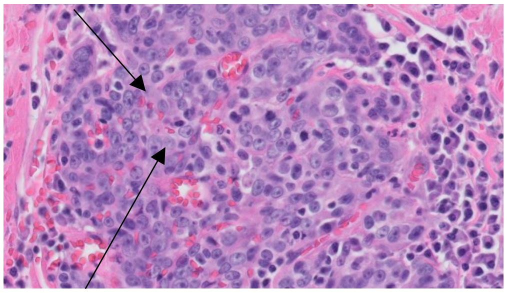
MORPHOLOGY

- **Malignant basaloid cells:** increased nuclear cytoplasmic ratio, **hyperchromatic irregular nuclei** with angulated edges, and **scant cytoplasm**
- **Myoepithelial cells: spindled** or **plasmacytoid**, some cytoplasmic clearing
- Scattered highly **atypical anaplastic giant cells** and **atypical mitoses**
- **Perineural** and **lymphovascular invasion** is usually **inconspicuous**
- Can be in cribriform, nests, or solid patterns, separated by fibrous stroma

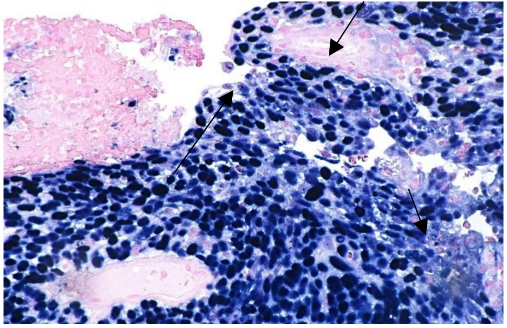
OTHER HIGH YIELD POINTS

- A rare subtype of non-keratinizing SCC with slight female predominance and occurs in the 5th decade with **majority** of cases **occur** in the **nasal cavity**
- **Can mimic adenoid cystic carcinoma**, which is a **potential pitfall**
- **Relatively indolent behavior** but has a potential **late recurrence (> 30 years)**
- **Immunohistochemistry:**
  - ➢ **Ductal epithelial cells:** positive for cytokeratin AE1/AE3, CD117, p16 (diffuse block positive)
  - ➢ **Myoepithelial cells:** positive for p40, p63, calponin, SOX10
- **Molecular:**
  - ➢ HPV-specific PCR positive for either: HPV-33, HPV-35, or HPV-52
  - ➢ No MYBL1-NFIB fusions

Sheets of cells


Abundant mitoses

EBER positive


EBER ISH provided by Nephron on Wikimedia

NASOPHARYNGEAL CARCINOMA

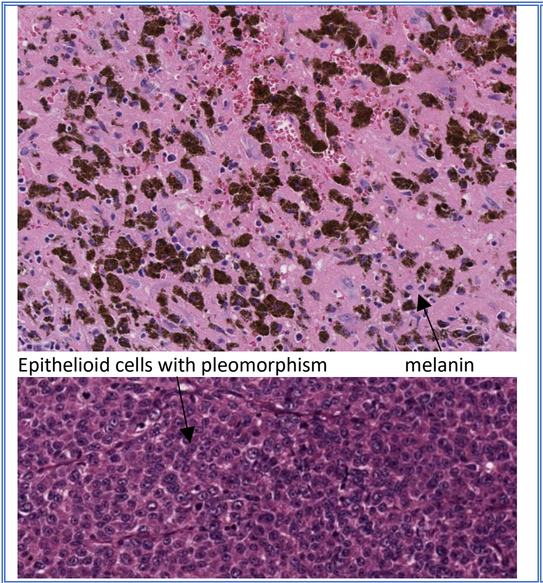
MORPHOLOGY

- **Non-keratinizing type: Majority** of cases, sheets of malignant cells with vesicular chromatin, indistinct cytoplasm, and abundant tumor-infiltrating lymphoplasmacytic infiltrate
- **Keratinizing type:** Similar microscopic features as keratinizing squamous cell carcinoma in other sites of the head and neck, surface epithelium involvement is frequently noted
- Abundant **mitoses** and **necrosis** are present

OTHER HIGH YIELD POINTS

- Usually in **middle-age to elderly males** with a **high prevalence** in **East Asia**, **Southeast Asia**, **North Africa**, and in the **Arctic**
- Presents as **cervical metastases**, has cranial nerve involvement in late stage
- Strong association with **EBV and nitrosamine exposure**
- Most cases will have **elevated EBV titers** in **serum** or **plasma**
  - ➢ Can be used for screening or marker for relapse
- **EBV-positive lesions** are **more radiosensitive**
- **Keratinizing type is more locally aggressive** and **non-keratinizing** type has more **frequent metastases**
- **Immunohistochemistry**: positive for pancytokeratin, p16
- RNA in situ hybridization: EBER positive

Path Presenter



MUCOSAL MELANOMA

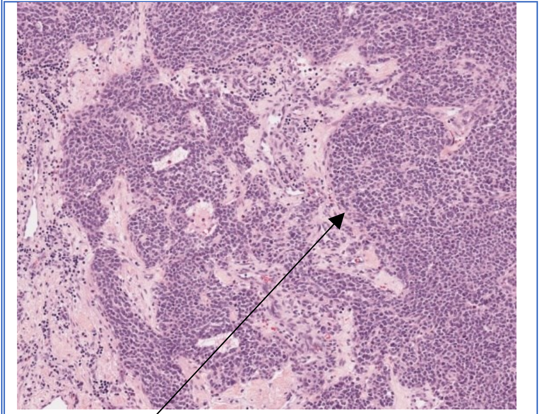
MORPHOLOGY

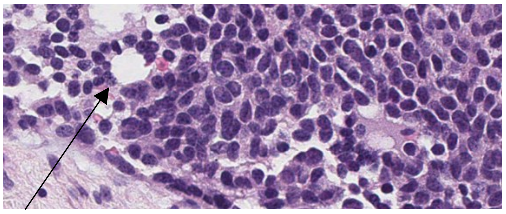
- **Epithelioid to spindled cells** with **pleomorphic nuclei** and often **prominent nucleoli** - variable morphology and architectural patterns
- Can have **peritheliomatous growth** with tumor cells arranged around vessels with background necrosis
- **Intracytoplasmic melanin** can be seen

OTHER HIGH YIELD POINTS

- Usually seen in **elderly patients** with **equal sex distribution**
- **Possible formalin** environmental **exposure risk**
- **Biologically distinct from cutaneous melanomas**
  - ➢ Must exclude metastatic melanoma clinically → neural crest derived
- **Poor prognosis** with recurrences being common
- Clark/**Breslow depth are not prognostic** and **not measured** in staging
- **IHC:** positive for S100, SOX10, HMB45, MelanA/MART1, MITF, Tyrosinase
- **Molecular: KIT** and **NRAS** mutations more common than BRAF

Path Presenter





OLFACTORY NEUROBLASTOMA (ESTHESIONEUROBLASTOMA)

MORPHOLOGY

- **Lobulated** nests to sheets of cells with **speckled chromatin, high N:C ratio**
- Fibrillary cytoplasm that resembles **neuropil**
- Can see either Homer-Wright **pseudorosettes** (lower grade neoplasms) and true Flexner-Wintersteiner rosettes (higher grade neoplasms)
- Higher grade neoplasms may not have the classical features and present as solely a **pleomorphic round blue cell tumor** with necrosis and mitoses

OTHER HIGH YIELD POINTS

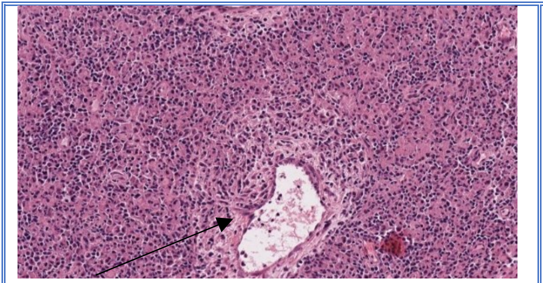
- Malignant neuroectodermal neoplasm c**onfined to the cribriform plate** (and surrounding region, including superior nasal concha, the upper part of the septum, and roof of nose)
- **Varied age range in typical patient population** with **slight male predilection**
- Radiologically described as a "**dumbbell-shaped**" **mass** in **cribriform plate**
- **Prognosis dependent** on **stage** and **grade** (Hyam's)
- **IHC:** positive for synaptophysin, chromogranin, CD56 (diffuse), calretinin, S100 (sustentacular pattern); negative for cytokeratin, FLI1, CD99, CD45RB
- **Electron microscopy:** Membrane bound neurosecretory granules measuring 50-250 um in size
- **Molecular:** Mutations in PTCH1, GLI1, and GLI2 present in 70% of cases

Path Presenter

HYAM'S HISTOPATHOLOGICAL GRADES OF OLFACTORY NEUROBLASTOMA

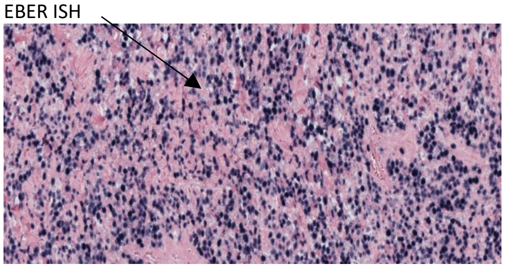
Grade	Lobular Preservation	Mitotic Index	Nuclear Pleomorphism	Fibrillary Matrix	Rosettes	Necrosis
I	Yes	None	None	Prominent	Homer-Wright	None
II	Yes	Low	Moderate	Present	Homer-Wright	None
III	No	Moderate	Prominent	Low	Flexner-Wintersteiner	Rare
IV	No	High	Marked	Absent	Flexner-Wintersteiner	Frequent

Adapted from: Hyams VG, Baksakis JG, Michaels L, eds. (1988). *Tumors of the upper respiratory tract and ear*. Washington DC: Armed Forces Institute of Pathology.



Angioinvasion

EBER ISH



EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

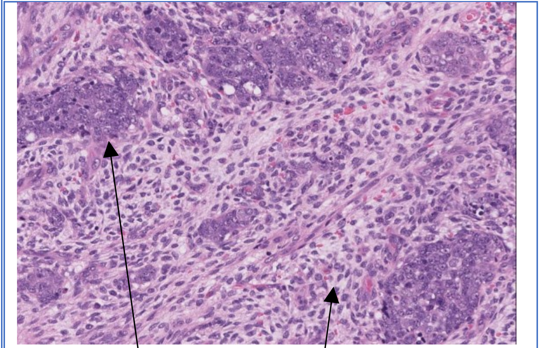
MORPHOLOGY

- Pleomorphic round blue cell tumor. Early disease can have malignant cells in large background of reactive lymphocytes
- Tumor cells have irregular borders and folding/cleaving/grooving are common features
- Characteristic angioinvasion and angiodestruction leading to necrosis

OTHER HIGH YIELD POINTS

- **Most common nonepithelial malignant neoplasm** in **sinonasal** tract
- More **frequent in Asian** and South American populations, typically middle age to elderly patient with male predilection
- Presents with **destructive pattern** in the sinonasal region
- **Poor prognosis** with good chance of relapse/recurrence
- Strong **association with EBV infection**
- IHC: positive for both T-cell and NK cell markers: **CD3+, CD56+, granzyme B+, EBER ISH+** in large majority

Path Presenter



Carcinomatous component Sarcomatous components

TERATOCARCINOSARCOMA

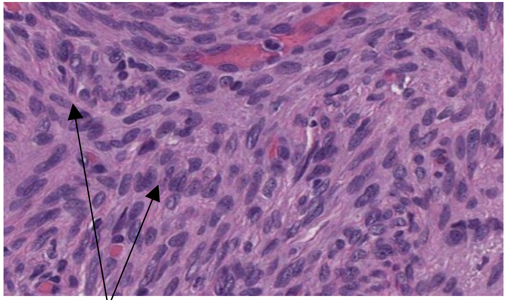
MORPHOLOGY

- **Carcinomatous and sarcomatous components** with either mature or **immature tissues from mesenchymal, epithelial**, or neuroepithelial lines
- If carcinomatous component is squamous, can have **"fetal" appearance** to tissue with glycogenated clear cell appearance

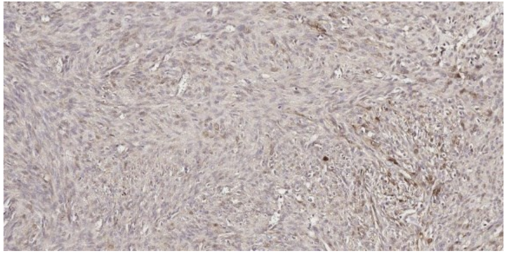
OTHER HIGH YIELD POINTS

- Rare neoplasm in sinonasal region with features of **teratoma** often including immature fetal-appearing squamous epithelium and **immature neuroepithelium as well as carcinosarcoma**
- Typically, **middle age to elderly males**
- **Aggressive tumor** with **poor prognosis** and **common recurrence**

Monotonous spindle cells



Intersecting fascicles



Variable S100 staining

BIPHENOTYPIC SINONASAL SARCOMA

MORPHOLOGY

- **Infiltrative monotonous spindle cell** neoplasm that has spindle cells with **elongated nuclei**, focally **irregular nuclear contours**, **variable chromatin** pattern, **eosinophilic cytoplasm**, and **indistinct cell borders**
- Spindle cells are arranged in **intersecting fascicles**, **herringbone**, **neural** and/or **myogenic differentiation**
- Associated with proliferation of respiratory glands
  - ➢ Dilated, benign glands with neoplastic stroma
- **Limited mitotic activity** and **no necrosis**

OTHER HIGH YIELD POINTS

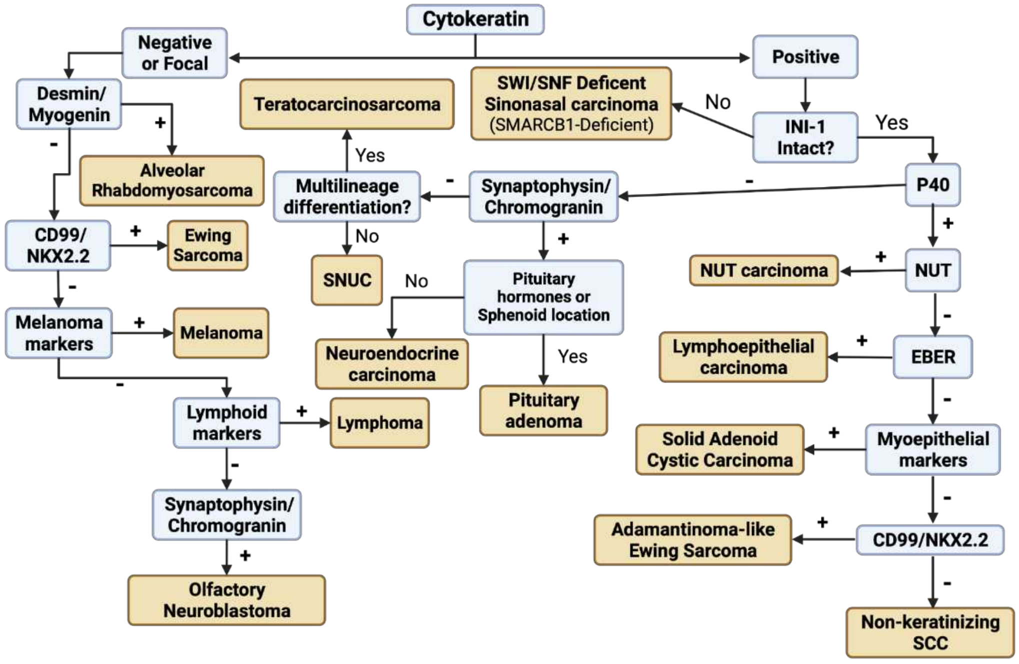
- **Rare neoplasm**, **only in sinonasal** region, typically **middle-aged females**
- **Locally aggressive** (with bone infiltration) but **non-metastatic**
- **Immunohistochemistry**:
  - ➢ Variable staining S100, SMA, nuclear β-catenin (focal to diffuse), desmin and myogenin; Negative for CD34
- **Molecular:** PAX3-MAML3 fusion → t(2;4)(q35;q31)
  - ➢ Other partners: NCOA1, FOXO1, WWTR1, NCOA2

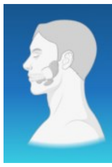
Path Presenter

USEFUL IMMUNOHISTOCHEMICAL STAINS FOR SINONASAL NEOPLASMS												
	SCC	**SNUC**	**SDSC**	**NUTC**	**HMSC**	**NPC**	**NEC**	**ME**	**RB**	**LYM**	**ONB**	**ES**
CK(AE1/AE3)	+	+	+	+	+	+	+	-	-	-	-	+/-
CK5/6	+	-	+/-	+	+	+	-	-	-	-	-	+/-
P63 and p40	+	-	+/-	+	+	+	-	-	-	-	-	+/-
Synapto/Chromo	-	-	-	-	-	-	+	-	+/-	-	+	+/-
CD56	-	-	-	-	-	-	+	-	+/-	+/-	+	+/-
CD99	-	-	-	-	-	-	-	-	-	+/-	-	+
P16	+/-	+/-	-	-	+	-	+/-	-	-	-	-	-
S100 **SOX10**	-	-	-	-	+	-	-	+	-	-	+	-
CD45	-	-	-	-	-	-	-	-	-	+	-	-
Myogenin/Desmin	-	-	-	-	-	-	-	-	+	-	-	-
NUT	-	-	-	+	-	-	-	-	-	-	-	-
INI-1	+	+	-	+	+	+	+	+	+	+	+	+
EBER	-	-	-	-	-	+	-	-	-	+/-	-	-

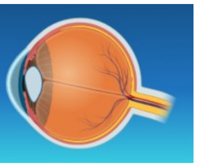
ABBREVIATIONS			
SCC	Squamous cell carcinoma	**NEC**	Neuroendocrine carcinoma
SNUC	Sinonasal undifferentiated carcinoma	**ME**	Mucosal melanoma
SDSC	SMARCB1(INI-1)-deficient sinonasal carcinoma	**RB**	Rhabdomyosarcoma
NUTC	NUT carcinoma	**LYM**	Lymphoma
HMSC	HPV-related multiphenotypic sinonasal carcinoma	**ONB**	Olfactory Neuroblastoma
NPC	Nasopharyngeal carcinoma	**ES**	Ewing sarcoma

Algorithm For Nasal Small Round Blue Cell Tumors

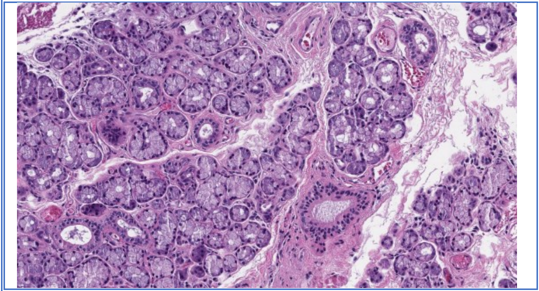

Cytokeratin
Negative or Focal
Positive
Desmin/ Myogenin
+
Alveolar Rhabdomyosarcoma
-
CD99/ NKX2.2
+
Ewing Sarcoma
-
Melanoma markers
+
Melanoma
-
Lymphoid markers
+
Lymphoma
-
Synaptophysin/ Chromogranin
+
Olfactory Neuroblastoma
Teratocarcinosarcoma
Yes
Multilineage differentiation?
No
SNUC
-
Synaptophysin/ Chromogranin
+
Pituitary hormones or Sphenoid location
No
Neuroendocrine carcinoma
Yes
Pituitary adenoma
SWI/SNF Deficent Sinonasal carcinoma (SMARCB1-Deficient)
No
INI-1 Intact?
Yes
P40
-
+
NUT
+
NUT carcinoma
-
EBER
+
Lymphoepithelial carcinoma
-
Myoepithelial markers
+
Solid Adenoid Cystic Carcinoma
-
CD99/NKX2.2
+
Adamantinoma-like Ewing Sarcoma
-
Non-keratinizing SCC



12. HEAD AND NECK PATHOLOGY



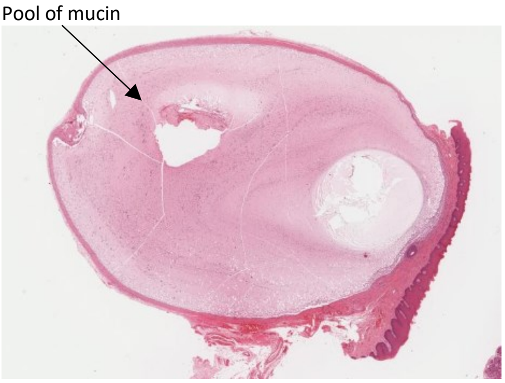
SALIVARY GLAND LESIONS



NORMAL SALIVARY GLAND

Normal components:

- **Ducts:** Interlobar, to intercalated, and striated with cuboidal to columnar epithelium, and surrounded by myoepithelial cells.
- **Acini:** Serous (parotid, with zymogen granules) to mucous (sublingual), surrounded by myoepithelial cells, look like grapes on cytology
- **Fat:** usually in parotid and lymph node (in parotid)
- If there is symmetric enlargement of salivary glands with no discrete mass, consider sialadenosis



MUCOCELE

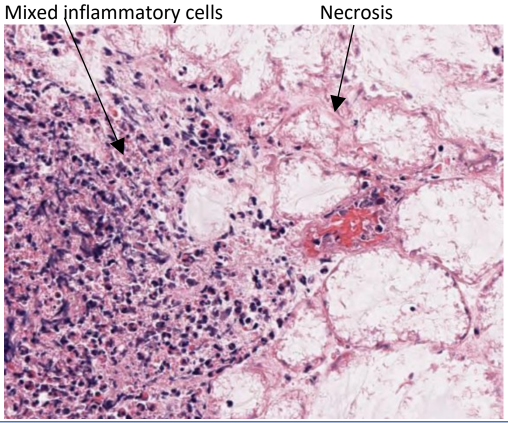
MORPHOLOGY

- **Pools of mucin** are walled off by granulation tissue which has abundant foamy macrophages
- **Histiocytes** may also be seen **within the mucin**
- There may be **overlying surface epithelial ulceration** if lesion is traumatized
- Mucin spillage may be seen or there may be ectatic ducts

OTHER HIGH YIELD POINTS

- Usually seen in **children and young adults** with a **slight male predominance**
- Most common site is the **lower lip**, less common is the floor of the mouth

Path Presenter



NECROTIZING SIALOMETAPLASIA

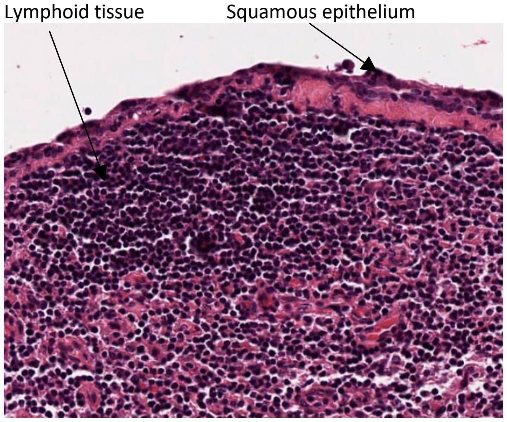
MORPHOLOGY

- **Lobular coagulative necrosis** of acini, **squamous metaplasia** of ducts, and **mixed inflammation**
- Overlying surface epithelium has **pseudoepitheliomatous hyperplasia** and may have **ulceration**

OTHER HIGH YIELD POINTS

- Can **occur in all ages** and **has a male predominance**
- Usually presents as a **unilateral lesion** of the **hard and soft palate** and affects the minor salivary glands
- **Resolves without treatment**

Path Presenter



LYMPHOEPITHELIAL CYST

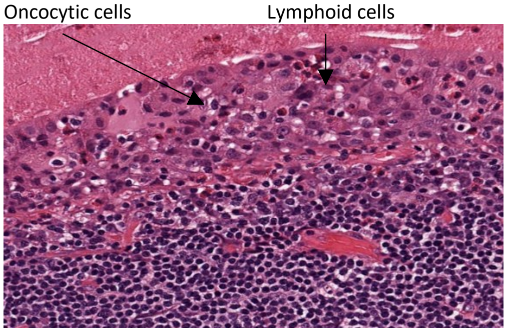
MORPHOLOGY

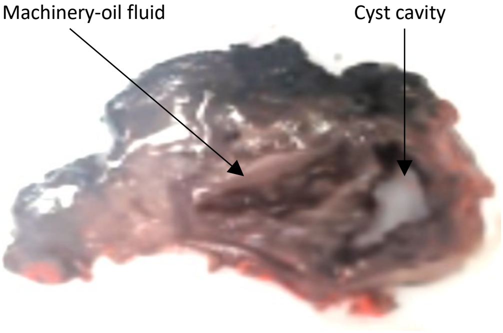
- Cyst **lined** by **squamous**, **ciliated**, **cuboidal**, or **columnar** epithelium
- Cyst **wall contains lymphoid tissue** with or without follicular hyperplasia
- **Lumen** has **desquamated squamous** cells

OTHER HIGH YIELD POINTS

- Typically seen in the **5th decade** with a slightly female predominance, but **HIV-associated lesions** are **more common in males**
- Usually asymptomatic but have compressible swelling overlying the parotid
- If **bilateral**, strongly **consider HIV infection**
- Surgical resection is curative

Path Presenter





PAPILLARY CYSTADENOMA LYMPHOMATOSUM (WARTHIN TUMOR)

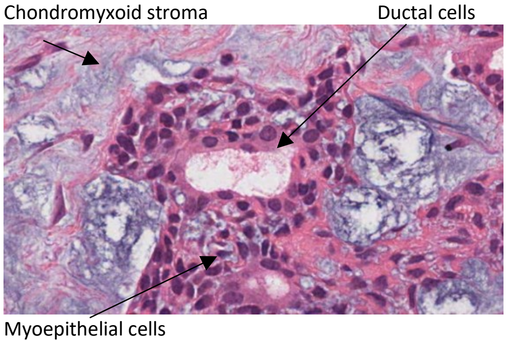
MORPHOLOGY

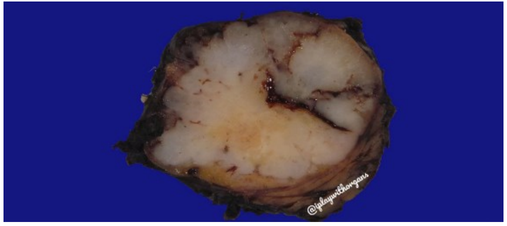
- **Cystic neoplasm** that is composed of two layers and line papillary projections:
  - **Inner layer of epithelial cells** are **non-ciliated columnar cells** that have round to **oval nuclei**, **conspicuous nucleoli**, and **oncocytic cytoplasm**
  - **Outer layer** is composed of **basal cells** that are **round or polygonal** cells with **vesicular nuclei** and **oncocytic cytoplasm**
- Wall contains mature l**ymphocytes** and may show **germinal centers**
- Cystic contents may include **cholesterol clefts**, **laminated bodies** (corpora amylacea-like), and or **thick secretory debris**
- Infarction, necrosis, squamous metaplasia, and cytologic atypia can be seen post-biopsy

OTHER HIGH YIELD POINTS

- **Most common** in the **6th decade** and **usually males**
- Presents as a **painless, slow-growing** parotid mass
- Nearly **10%** of all cases **are bilateral**
- Associated with **cigarette smoking**
- Gross examination shows a **cystic lesion**, **grungy and thick cystic fluid**
- Recurrence is variable

Path Presenter





PLEOMORPHIC ADENOMA

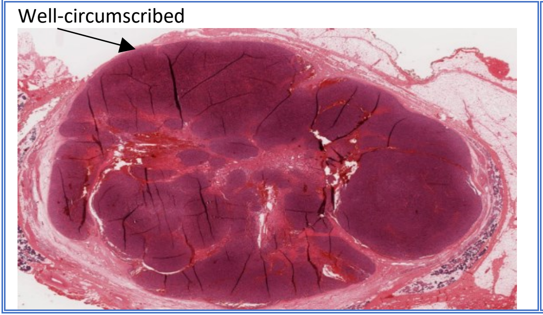
MORPHOLOGY

- Composed of **ductal cells, myoepithelial cells, and stroma**
- **Myoepithelial cells:** plasmacytoid, spindled, squamoid, basaloid, or stellate
- Background **stroma is variable** and can be **myxoid**, **mucoid**, **chondroid**, **hyalinized**, or **osseous**

OTHER HIGH YIELD POINTS

- **Most common** salivary gland **tumor**
- Usually seen in **middle-aged females**
- Presents as a **painless slow-growing mass** of the parotid gland
- Gross: **Well-demarcated**, **encapsulated** round/oval tumors
- **Recurrence rate: 20-45%, malignant transformation: 7%**
- **IHC**: Myoepithelial cells positive for S100, SOX10, P63, P40, SMA, Calponin, GFAP, CD10, cytokeratins, CK7 (plasmacytoid myoepithelial cells)
- **Molecular**: PLAG1-HMGA2 fusion

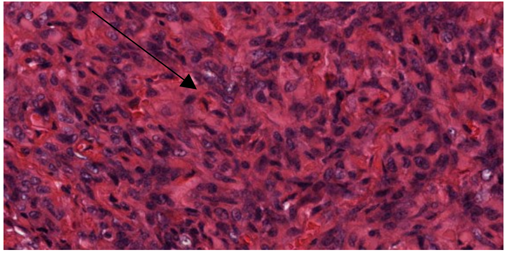
Path Presenter



MYOEPITHELIOMA

MORPHOLOGY

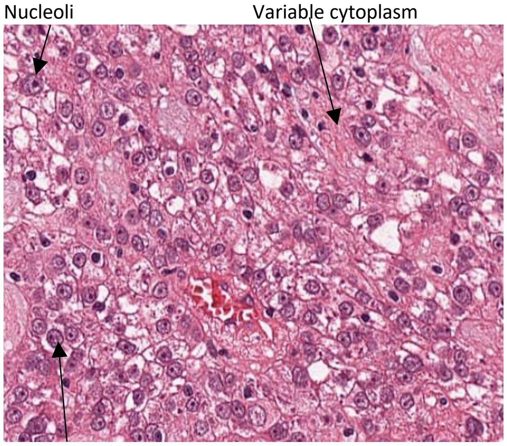
- **Myoepithelial cells** that are either **spindled**, **epithelioid**, or **plasmacytoid**
- The **plasmacytoid forms** will have **round to oval hyperchromatic nuclei**, and abundant **eosinophilic cytoplasm**
- Background **stroma is variable** and may have abundant **myxoid**, **myxochondroid**, or **chondroid** changes
- **Lacks** any evidence of **infiltrative borders**, **perineural** or **lymphovascular invasion**, **pleomorphism**, or **mitotic activity**
- **Well circumscribed** but may not always have a capsule



OTHER HIGH YIELD

- Most numerous cases in the **3rd to 4th decade**, with **equal sex distribution**
- Presents as an **asymptomatic painless**, slow growing **mass**
- Nearly 60% of cases occur in the parotid gland, remaining in hard/soft palate
- **IHC**: Positive for pancytokeratin, CK7, p40, p63, GFAP, S100 protein, and variable actins
- Molecular: Lacks PLAG1 mutations

Path Presenter



MYOEPITHELIAL CARCINOMA

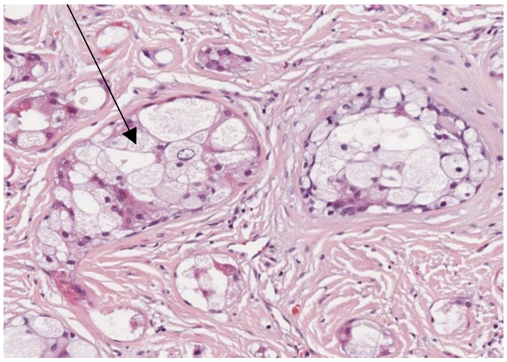
MORPHOLOGY

- **Myoepithelial** cells that are either **spindled, epithelioid, or plasmacytoid**
- Have **conspicuous nucleoli**, **irregular** nuclear **contours**, **variable cytoplasm**
- Frequently has **perineural** or **lymphovascular invasion**
- **Necrosis**, **atypical mitotic figures**, and **invasive borders** are seen

OTHER HIGH YIELD

- **Uncommon malignant lesion** occurring **6th decade, no sex predilection**
- Presents as a **slow growing**, **painless mass** or may be **painful**
- **Survival is fair** with **~65% at 5 years** and **recurrence is common (50%)**
- **Metastasis** (locally) is the **cervical neck**; **distant metastasis** is usually the **lung**
- **IHC**: Positive for CK5/6, p63, S100 protein, and actins
- **Molecular: TGFBR3-PLAG1 fusion (unique)**

Path Presenter



SEBACEOUS ADENOMA

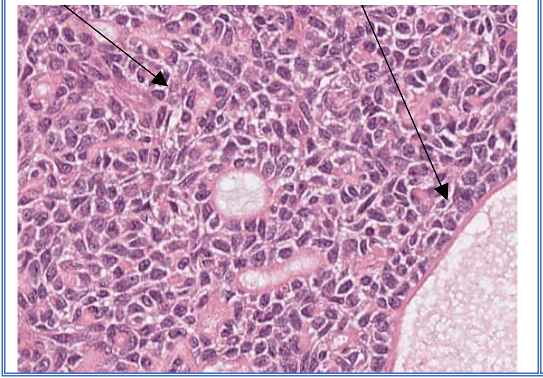
MORPHOLOGY

- Epithelial cells with **sebaceous differentiation** and are often **arranged** in **small clusters** or **lining a cystic space**

OTHER HIGH YIELD POINTS

- Usually occurs in **6th-7th decade** and has **no gender predilection**
- Presents as a **slow growing mass**
- Most common in **major salivary glands** (parotid)
- Gross: **Well circumscribed** pink or gray solid/cystic mass
- Recurrence is rare

Path Presenter



BASAL CELL ADENOMA

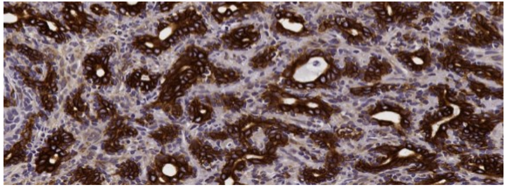
MORPHOLOGY

- Peripheral **basaloid cells** with **scant cytoplasm** and **basophilic nuclei** and **central cells with abundant cytoplasm** and round **pale nuclei** which can have ductal structures or squamous metaplasia
- **Subtypes**: Solid, tubular, trabecular, or membranous

OTHER HIGH YIELD POINTS

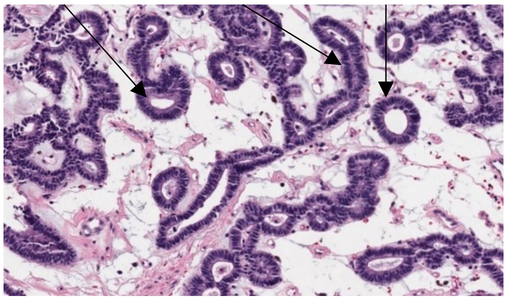
- Parotid tumor occurring in **6th decade**, **subtypes seen differ by gender**
  - **Females**: Solid, tubular, or trabecular
  - **Males**: membranous
- Gross: **Well-circumscribed** encapsulated epithelial tumor
- **Immunohistochemistry**:
  - **Central cells**: positive for Cytokeratin cocktail, CD117, and CK7

IHC: Cytokeratin CAM 5.2



  - ➢ **Peripheral cells**: positive for SOX10, S100, P63, SMA, β-catenin (nuclear)
- Membranous type has a 25% recurrence rate and small risk of malignant transformation

Path Presenter



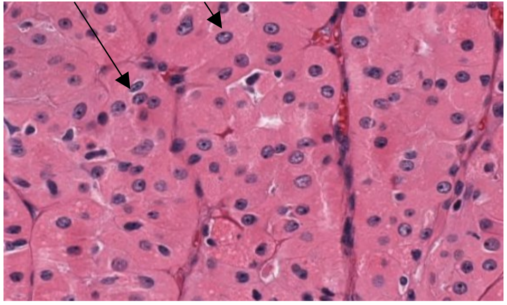
CANALICULAR ADENOMA

MORPHOLOGY

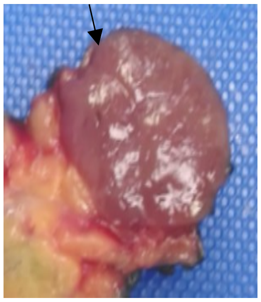
- **Cuboidal to columnar cells** that are **cytologically bland** and **form tubules**, **ducts**, or **solid** groups
- The background is **loose collagenous stroma**

OTHER HIGH YIELD POINTS

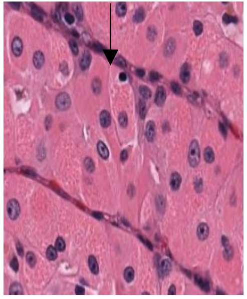
- Usually seen in **elderly black females** in the **minor salivary glands**
- Most common site is the **upper lip** and presents as a **multinodular mass**
- Gross: Circumscribed, unencapsulated, solid/cystic, pink-tan up to 2 cm
- **Recurrence is rare**
- **IHC**: **Positive** for **Cytokeratin** and **S100**; **GFAP positive** at tumor **interface**



Round red-brown cut surface



Trabecular pattern



ONCOCYTOMA

MORPHOLOGY

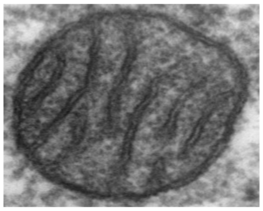
- **Polygonal cells** with **round nuclei**, **conspicuous nucleoli**, and **abundant granular**, **eosinophilic cytoplasm**
- Arranged in **solid**, **trabecular**, **acinar**, or **follicular** architecture

OTHER HIGH YIELD POINTS

- Usually seen in **elderly white females**
- Most **common location** is the **parotid** followed by submandibular
- Presents as a **slow growing mass**
- Gross: Solitary **well-circumscribed tan-brown mass**/nodule
- **Low risk of recurrence** post-excision
- **IHC**: positive for cytokeratin, p63, **phosphotungstic acid-hematoxylin**
- **Electron microscopy:** Abundant mitochondria

Path presenter

Mitochondria on EM



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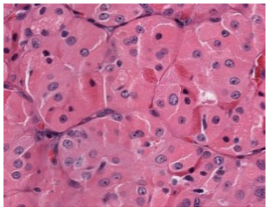
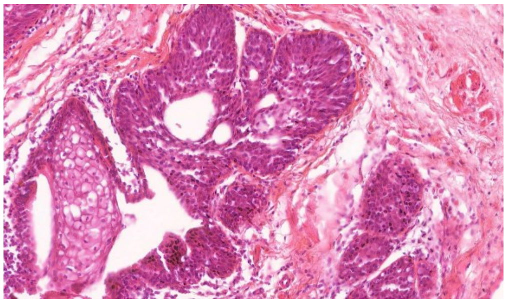
Acinar pattern





No evidence of invasion

SQUAMOUS METAPLASIA

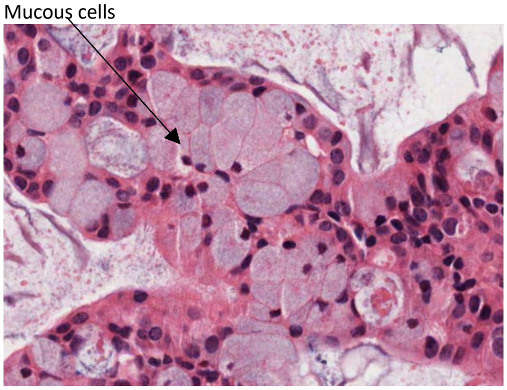
MORPHOLOGY

- Classic **mimic of squamous cell carcinoma**
- **Lobular architecture** is **maintained**
- Nuclei have **mild pleomorphism**, no atypical mitoses though
- Nests have **smooth and rounded edges**
- Often **associated inflammation** and **reactive changes**
- Acinar **coagulative necrosis**

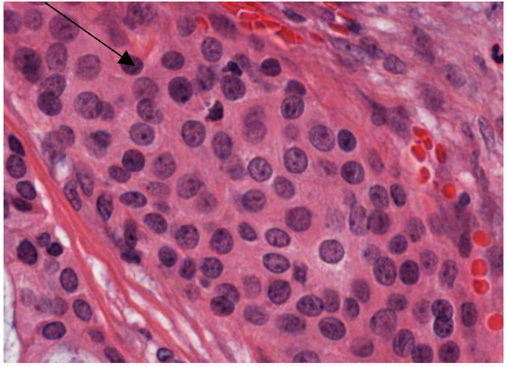
OTHER HIGH YIELD POINTS

- Can see in **normal salivary glands** or tumors (e.g., PA)
- In minor salivary gland often called: "**Necrotizing sialometaplasia**"
- Be cautious and do not overcall squamous cell carcinoma

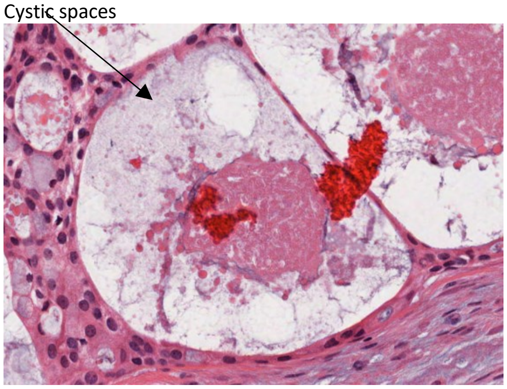
Mucous cells



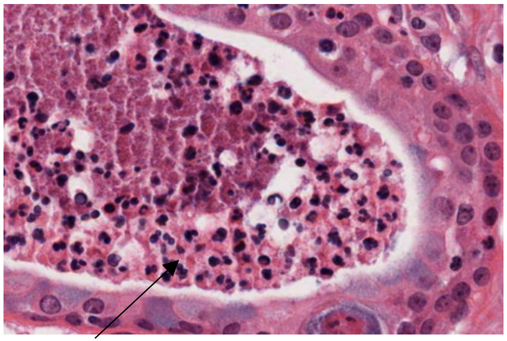
Squamoid cells



Cystic spaces



Necrosis



Degenerating debris

MUCOEPIDERMOID CARCINOMA

MORPHOLOGY

- Composed of a mixture of malignant cells and cystic spaces:
    - ➢ **Squamoid cells:** polygonal cells with round to oval nuclei, conspicuous nucleoli, and eosinophilic cytoplasm; **keratinization is uncommon**
    - ➢ **Mucous cells:** cells with **intracytoplasmic vacuoles** containing **mucin** and resemble goblet cells
    - ➢ **Intermediate cells:** Large polygonal cells and **small basaloid cells** and are typically seen in **sheets or nests**
    - ➢ **Cystic spaces:** Occasionally have papillary projects and mucin is often present
- If **mucin** is present **extracellularly**, expect **associated inflammatory response**
- There may be **necrosis**, **atypical mitotic figures**, or **invasion**

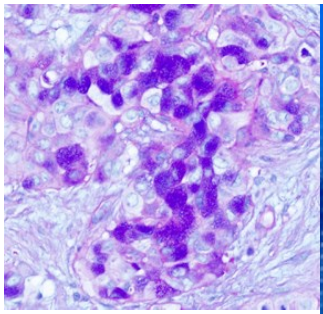
OTHER HIGH YIELD POINTS

- **Most common salivary** gland **malignancy**
- Usually seen in **middle aged females**
- **Most common** the **major salivary glands (parotid)**
- Gross: **Encapsulated**/**circumscribed**/**infiltrative** tumor that is **less than 4cm** with cysts that contain brown fluid
- **Most** tumors are **low-grade**
- **Submandibular** location has a **worse prognosis**
- **IHC**: Intermediate and epidermoid cells are positive for cytokeratin, p40, p63, EMA, and p16 (unrelated to HPV); high grade positive for HER2
- Molecular:
    - ➢ **CRTC1-MAML2 fusion → t(11;19)(q21;p13)** and is seen in 60% of cases
    - ➢ **CRTC3-MAML2 fusion →** t(11;15)(q21;q26) is usually **younger patients**
    - ➢ Aggressive tumors frequently show copy number alterations of CDKN2A
    - ➢ High-grade tumors frequently have a TP53 mutation or increased ERBB2 or EGFR copy number alterations

Parameters for Grading	Points
Cystic component < 20%	2
Neural invasion	2
Necrosis	3
Mitotic figures > or = to 4/10 HPFs	3
Anaplasia	4

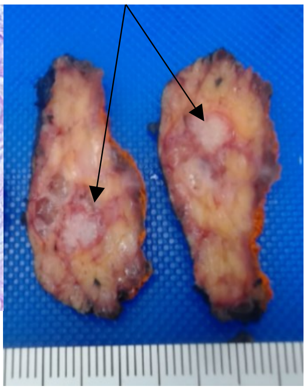
Grade	Score
Low	0-4
Intermediate	5-6
High	≥ 7

Alcian Blue-PAS Stain



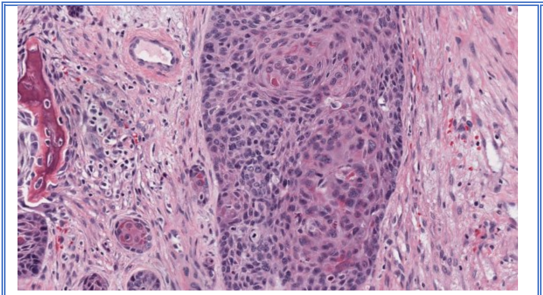
AB-PAS by: KGH on Wikimedia

Infiltrative



Path Presenter

12. HEAD AND NECK PATHOLOGY



SQUAMOUS CELLS CARCINOMA

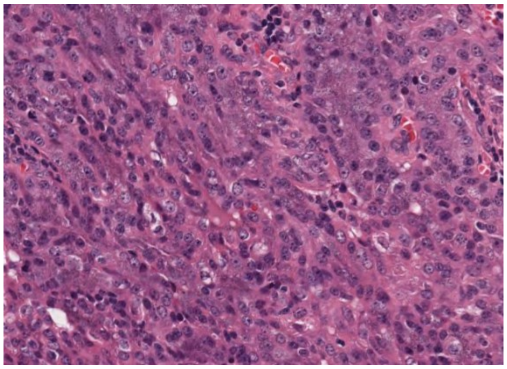
MORPHOLOGY

- High grade mucoepidermoid carcinomas often are more squamous, so make sure the tumor is well-sampled

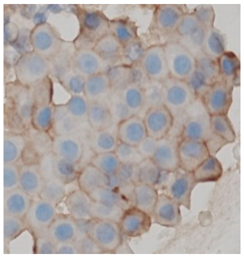
OTHER HIGH YIELD POINTS

- If it is **entirely squamous** (with no **mucinous cells or intermediate** cells, and when there are keratin pearls), a **metastasis needs to be excluded** clinically- often actually a metastasis from a Head or Neck squamous cell carcinoma
- Also consider extensive SCC differentiation of another salivary gland carcinoma

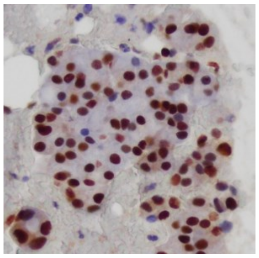
Serous acinar cells



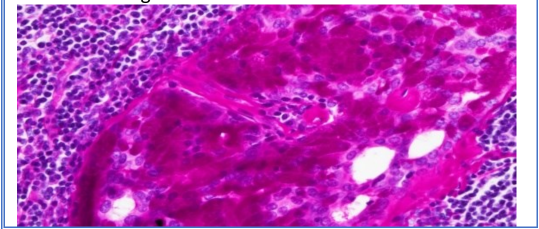
DOG1 IHC



NR4A3 IHC



PASD Positive granules



ACINIC CELL CARCINOMA

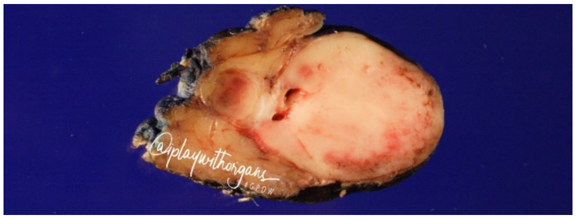
MORPHOLOGY

- Variable morphology of the cells:
  - ➢ **Serous acinar (most common):** uniform to round eccentrically located nuclei, variable chromatin pattern, and basophilic coarse zymogen granules in cytoplasm
  - ➢ **Intercalated duct type:** Cuboidal cells with centrally located nuclei and eosinophilic to amphophilic cytoplasm
  - ➢ **Vacuolated:** cells have clear cytoplasm with intracytoplasmic vacuoles
  - ➢ **Non-specific glandular:** polygonal cells with variable nuclei, and amphophilic to eosinophilic cytoplasm
- Patterns are variable: **solid/lobular** (most common), **microcystic**, **papillary-cystic**, and **follicular**

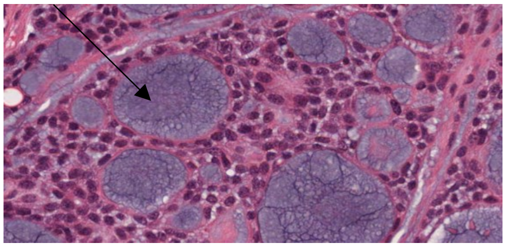
OTHER HIGH YIELD POINTS

- Usually seen in **females with a wide age distribution**
  - ➢ **Second most common malignant** salivary **neoplasm** in **children**
- **Parotid gland** most **common location**
- Presents as a **slow growing mobile/fixed mass,** may be bilateral/multifocal
- Gross: **Circumscribed tumors** less than 3 cm with rubbery to firm consistency and cystic/hemorrhagic areas
- **Recurrence rate** is approximately **33%**
- **IHC:** positive for **DOG1**, **SOX10**, and **NR4A3 (most specific)**
- **Molecular**: **NR4A3 translocation** → t(4;9)(q13;q31)

Path Presenter



Matrix material



S100 IHC

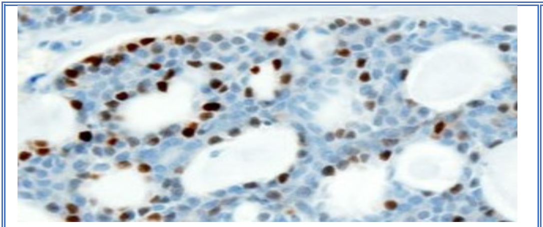
ADENOID CYSTIC CARCINOMA

MORPHOLOGY

- **Malignant epithelial cells** and **myoepithelial cells** that are arranged in **tubules**, **cribriform**, **cylindromatous**, and **solid** patterns
- There is intraluminal **basophilic matrix** and **basement membrane material**
- Usually has **extensive perineural invasion**

OTHER HIGH YIELD POINTS

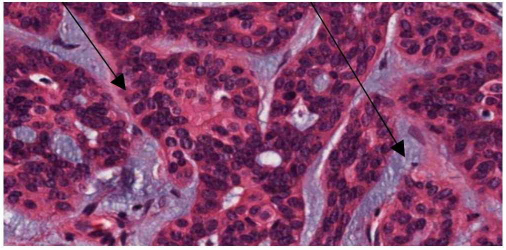
- Usually seen in **middle age to elderly adults** with **female predilection**
- Presents as a **slow growing parotid mass**
- **Prognostic factors:** size, site (submandibular worse), stage, pattern (solid worse), and high-grade transformation
- 5-year survival is 62%; 10-year survival is 40%

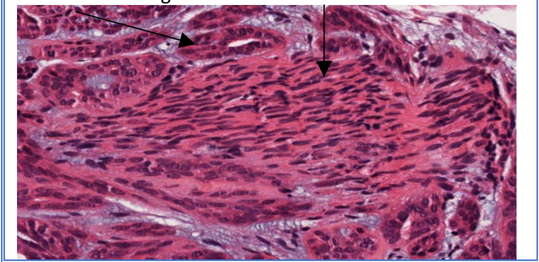


By: KGH on Wikimedia

- **Immunohistochemistry**:
  - **Myoepithelial cells**: positive for P40, SMA, S100, Calponin, and P63
  - **Ductal cells:** positive for CD117, EMA, and LMWCK
- **Special stains**: Matrix material is PAS and Alcian Blue positive
- **Molecular**: MYBL1-NFIB fusion → t(6;9)(q22-23;p23-24)

Path Presenter





POLYMORPHOUS ADENOCARCINOMA

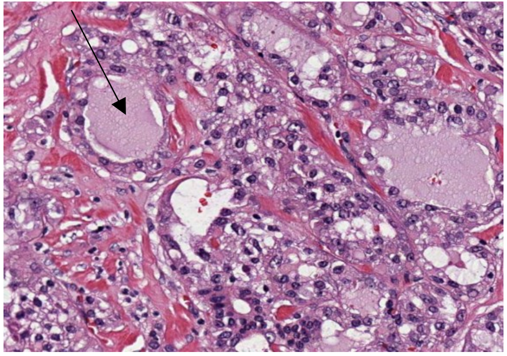
MORPHOLOGY

- **Cells are monotonous** with vesicular, **round to oval nuclei**, and have **eosinophilic cytoplasm**
- **Variable architecture**, including **cribriform**, **single-file, tubular**, and **trabecular** with concentric arrangement around nerves.
- **Intervening stroma** can be **hyalinized**, **myxoid**, or **mucinous**.
- Mitoses and necrosis are only seen in high grade tumors

OTHER HIGH YIELD POINTS

- Usually seen in **elderly females** and most common site is the **palate**
- Presents as an **asymptomatic slow growing mass**
- Gross: Well circumscribed, unencapsulated yellow or tan mass
- **Prognosis excellent** and has a low recurrence rate about 10%
- **IHC**: positive for cytokeratin, S100, SOX10, vimentin; variable p63; P40 (-)
- **Molecular**: Activating hotspot mutations in **PRKD1 in nearly 75% of cases**

Path Presenter



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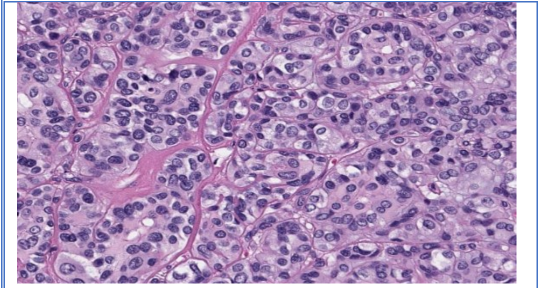
SECRETORY CARCINOMA (MAMMARY ANALOGUE SECRETORY CARCINOMA)

MORPHOLOGY

- Malignant **epithelial cells** with uniformly round nuclei with no significant pleomorphism, **small nucleoli**, **vacuolated eosinophilic cytoplasm** containing **secretory material**
- Lumina contains **dense eosinophilic secretions**
- May be in a **solid**, **tubular**, or **microcystic pattern**

OTHER HIGH YIELD POINTS

- Usually is seen in **middle-aged males** with an **asymptomatic parotid mass**
- Tumors with **high-grade transformation** are **more likely** to **have recurrence** and **regional lymph node involvement**
- **IHC**: Positive for S100, SOX10, mammaglobin, Pan-TRK, and GCDFP15
- **Special stains**: Secretory material is **PASD positive**
- **Molecular**: **Balanced translocation** of t(12;15)(p13;q25) → **ETV6-NTRK3**
- **FISH**: Break apart probes for ETV6



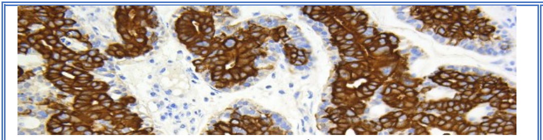
EPITHELIAL MYOEPITHELIAL CARCINOMA

MORPHOLOGY

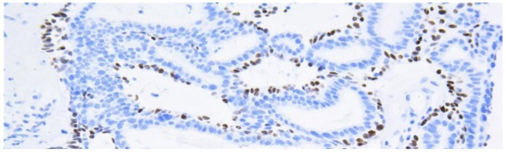
- Composed of two cell types:
  - **Inner ductal cells** with round to ovoid nuclei, inconspicuous nucleoli, and eosinophilic to amphophilic cytoplasm
  - **Outer myoepithelial cells** with vacuolated cytoplasm

OTHER HIGH YIELD POINTS

- Usually seen in **elderly females** and present as a **slow growing mass**
- Gross: Circumscribed and lobulated but unencapsulated with cystic areas
- **Good prognosis with an 80% 5-year survival rate**; **recurrence** rate: **40%**



IHC: CK AE1/AE3



IHC: p40

- **Poor prognosis** for those with **large tumors**, **fast growing** tumors, **incomplete excision**, and tumors that are **in the minor salivary glands**
- **Immunohistochemistry:**
  - **Myoepithelial cells:** positive for SMA, p63, p40, CD117, and BCL2
  - **Ductal cells:** positive for keratins
- **Molecular**: **HRAS mutations** in 33% of cases
  - PLAG1-HMGA2 mutations seen in those originating from PA

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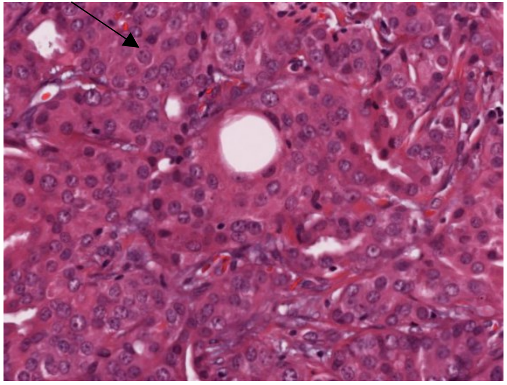
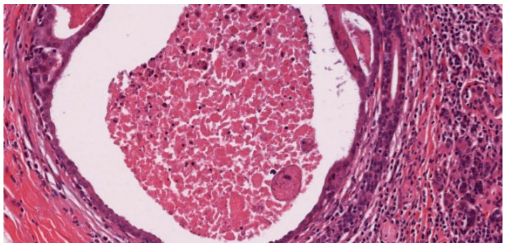
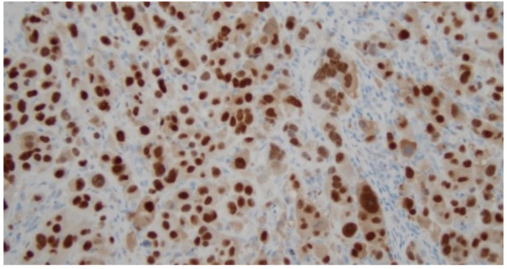
Variable nuclear pleomorphism



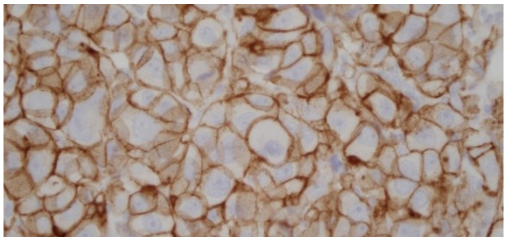
Comedonecrosis



Androgen Receptor IHC



HER2 IHC



SALIVARY DUCT CARCINOMA

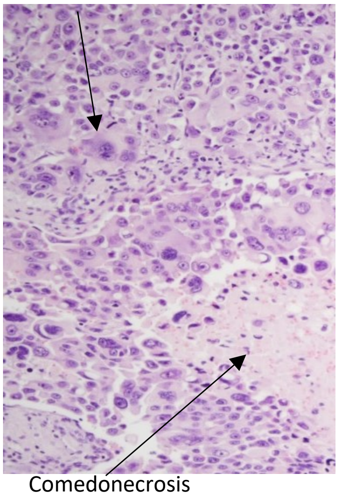
MORPHOLOGY

- **Resembles invasive breast carcinoma** of no special type
- Composed of **nests** or **cystic nodules** of **tumor cells** with **variable nuclear pleomorphism**, and **abundant apocrine cytoplasm**
- **Comedonecrosis** is **present** within the lumens
- **Perineural invasion** is **common** and **lymphovascular invasion** can be **seen**
- Can have **dense fibrosis** and **inflammatory infiltrate**

OTHER HIGH YIELD POINTS

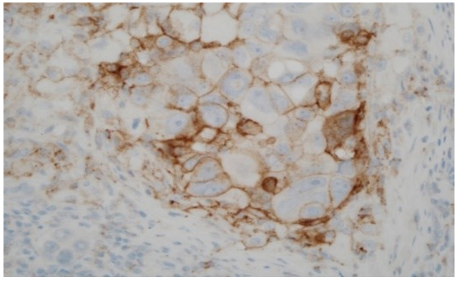
- Usually seen in **elderly males** and **most common in** the **parotid**
- Presents as a **painful**, **rapidly growing mass**
- Gross: **Infiltrative white/gray mass** with **necrosis**, **hemorrhage**, and **cysts**
- **Regional metastasis** is seen in **60%** and **distant spread** in **50% of cases**
- **Size** is also a **prognostic** factor besides **distant metastasis**
- **IHC**: Positive for **AR**, **CK7**, CEA, and EMA; Negative for CK5/6, p63, ER,PR; **HER2 positive in ~33%** of cases; variable PDL1
- **Molecular**: **TP53** is the most common mutation, other alterations include **PIK3CA**, **HRAS**, **ERBB2**, PTEN, ALK, BRAF, and MYC
  - PLAG1 or HMGA2 are seen in cases arising from pleomorphic adenoma

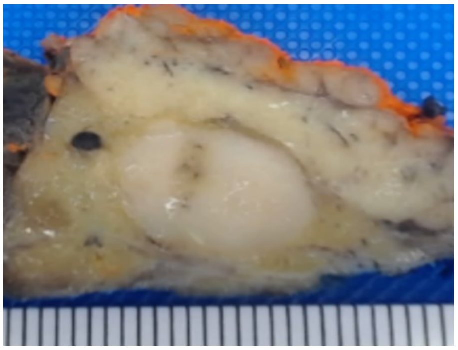
Pleomorphism



Comedonecrosis

PDL1 IHC





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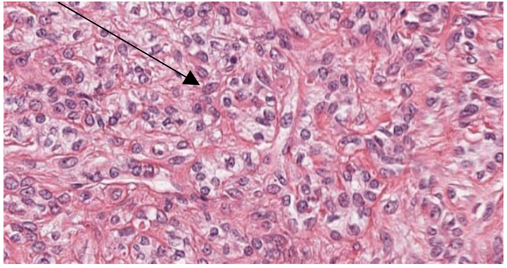
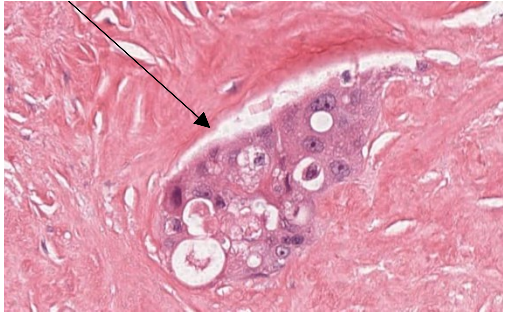


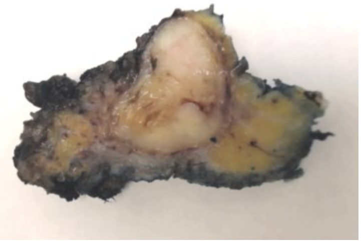


CARCINOMA EX PLEOMORPHIC ADENOMA

- **Preexisting pleomorphic adenoma** with a **carcinomatous component**, usually a salivary duct carcinoma
- **Carcinomatous components** can be **epithelial**, **myoepithelial**, or a **mixture of both**

OTHER HIGH YIELD POINTS

- Usually seen in **elderly patients** with no sex predilection
- **Most common** location is the **parotid** gland
- Presents as a **long-time mass** that **suddenly grows**
- **Prognosis**:
  - Minimally invasive tumors (<4-6mm) → good
  - Invasive tumors (>4-6mm) → poor
- **Molecular**: Various mutations
  - **PLAG1, HMGA2**
  - HMGCIC, MDM2
  - HER2 amplification
  - TP53 mutations
  - Copy number gains of 9p, 22q



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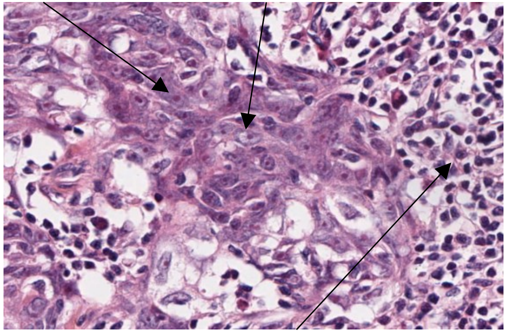

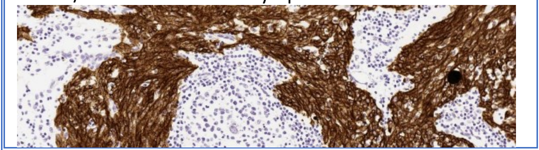

LYMPHOEPITHELIAL CARCINOMA

MORPHOLOGY

- **Sheets** and **cords** of **polygonal large syncytial cells** with **eosinophilic cytoplasm** and **vesicular nucleoli**
- Scattered **spindle cells**
- Abundant **lymphoplasmacytic infiltrate**

OTHER HIGH YIELD POINTS

- **Rare tumor** which has the **highest incidence** in the **Arctic Inuit**
- Usually occurs in **middle aged** individuals
- Most commonly affects the **major salivary glands** (parotid> submandibular)
- Presents as **non-specific swelling** that may be painful
- **Survival** is fair, **80% at 5-years**
- **IHC**: positive for **CKAE1/AE3**, **CK903,** SOX10, CD117, **EBV-LMP1**
- RNA in situ hybridization: **positive for EBER**

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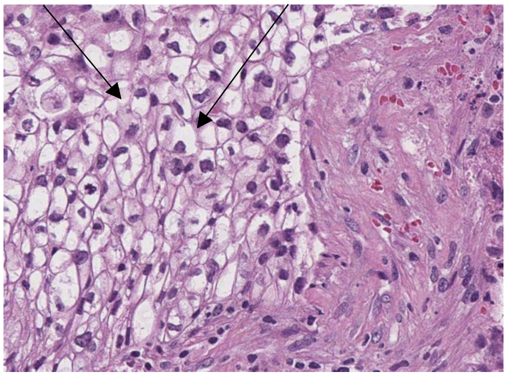


HYALINIZING CLEAR CELL CARCINOMA

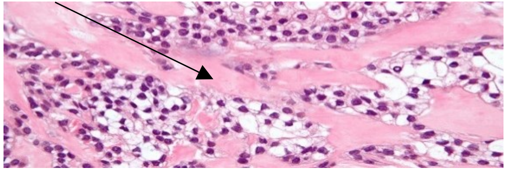
MORPHOLOGY

- **Malignant cells** with **eccentrically located nuclei** with **irregular** nuclear **contours**, **clear cytoplasm**, and **well-defined cell borders**
- Malignant cells are in **sheets**, **nests**, or **trabeculae**
- Tumor nests are separated by **hyalinized stroma**
- **Perineural invasion** is **common** and easily identified

OTHER HIGH YIELD POINTS

- **Rare carcinoma** with a **female predominance** and a **wide age range**
- Most **common** in **minor salivary** glands
- Presents as a **dome-shaped** or **sessile mass** with overlying ulceration
- **IHC**: positive for **cytokeratins**, **CK5/6**, **p40**, **p63**; negative for S100 protein, SOX10, SMA, calponin
- **Special stains**: **PAS positive** due to the glycogen in the cells

Hyalinized stroma



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- **Electron microscopy**: Tonofilaments and microvilli are seen →look at desmosomes and tight-junctions
- **Molecular**: **EWSR1-ATF1** fusion → **t(12;22)(q13;q12**) is seen in a majority of cases

Path Presenter

USEFUL IMMUNOHISTOCHEMICAL MARKERS FOR HIGH-GRADE SALIVARY NEOPLASMS							
	P63/p40	**SMA, Calponin**	**CK8/18**	**CK5/6**	**Mucin**	**AR**	**Synaptophysin**
Mucoepidermoid, High-grade	+	-	**Focal**	+	+	-	-
Squamous cell carcinoma	+	-	-	+	-	-	-
Salivary Duct Carcinoma	-	-	+	-	-	+	-
Poorly differentiated neuroendocrine carcinoma	-/+	-	**Dot-like**	-	-	-	+

USEFUL IMMUNOHISTOCHEMICAL MARKERS FOR BASALOID SALIVARY NEOPLASMS								
	P63	**P40**	**SMA/Calponin**	**S100**	**CD117**	**LEF-1**	**PLAG1**	**MYB**
Pleomorphic adenoma	+	+	+	+	+/1	+/1	+	-
Basal cell adenoma/carcinoma	+	+	+	-/+	+/-	+	-	-
Adenoid cystic carcinoma	+/-	+/-	+	+	+	-	-	+
Myoepithelioma/carcinoma	+	+	+	+	-	-	-/+	-
EMEC	+	+	+	+	-/+	-	-	-
PLGA	+	-	-	+	+/-	-	+/-	-

USEFUL IMMUNOHISTOCHEMICAL MARKERS FOR CLEAR CELL SALIVARY NEOPLASMS				
	P63/p40	**S100**	**SOX10**	**DOG1**
Myoepithelioma/carcinoma	+	+	-	-
EMEC	+	+	-	-
Acinic cell carcinoma	-	-	+	+
Mucoepidermoid carcinoma	+	-	-/+	-/+

USEFUL IMMUNOHISTOCHEMICAL MARKERS FOR ONCOCYTIC SALIVARY NEOPLASMS								
	P63	**P40**	**S100**	**Mammaglobin**	**SOX10**	**DOG1**	**GATA3**	**AR**
Warthin & Oncocytoma	+	-	-	-	-	-	-	-
Acinic cell carcinoma	-	-	-	-	+	+	-	-
Secretory carcinoma	-	-	+	+	+	-	+	-
Mucoepidermoid carcinoma	+	+	-	-	-/+	-/+	-	-
Salivary duct carcinoma	-	-	-	-/+	-	-	+	+

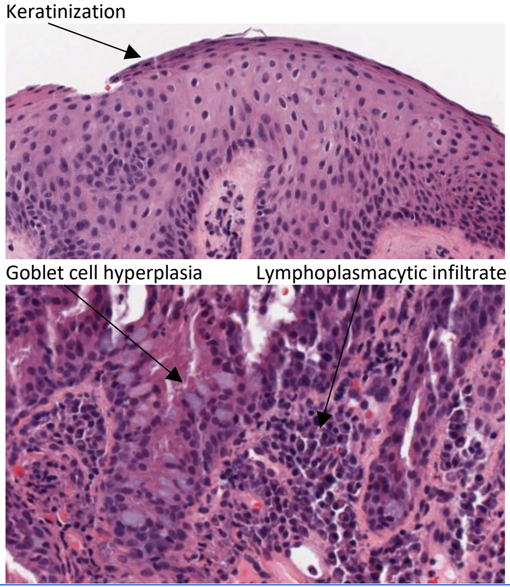
MOLECULAR FINDINGS IN SALIVARY NEOPLASMS		
TUMOR	**MOST COMMON MOLECULAR ALTERATION**	**INTERNATIONAL SYSTEM NOMENCLATURE**
Adenoid cystic carcinoma	MYB fusions	t(6;9)(q22-23;p23-24)
Hyalinizing clear cell carcinoma	EWSR1-ATF1 Fusion	t(12;22)(q13;q12)
Intraductal carcinoma	NCOA4-RET fusions	NCOA4::RET (Chromosome 10)
Mucoepidermoid carcinoma	CRCT1-MAML2 fusions	t(11;19)(q21;p13)
Pleomorphic ademoma	PLAG1-HMGA2 fusions	t(8;12)(q12;q14.3)
Polymorphous low-grade adenocarcinoma	PRKD E710D	Not applicable
Secretory carcinoma	ETV6-NTRK3 fusions	t(12;15)(p13;q25)
Acinic cell carcinoma	NR4A3 translocations	t(4;9)(q13;q31)
Epithelial-Myoepithelial Carcinoma	PLAG1-HMGA2 or HRAS mutations	t(8;12)(q12;q14.3)
Myoepithelial Carcinoma	TGFBR3-PLAG1 translocations (Unique)	t(1;8)(p22.1;q12.1)
Basal cell adenoma/adenocarcinoma	CTNNB1 or CYLD mutations	Not applicable

CLASSIFICATION OF SALIVARY GLAND NEOPLASMS BY GRADE			
Low-grade (treated surgically like benign tumors)	**Intermediate (treated variably)**	**High-grade (Treated aggressively)**	**Variable grade**
Acinic Cell Carcinoma Polymorphous Adenocarcinoma Basal cell adenocarcinoma Epithelial-Myoepithelial Carcinoma Secretory carcinoma Clear Cell Carcinoma	Myoepithelial Carcinoma	Salivary Duct Carcinoma Neuroendocrine carcinoma Lymphoepithelial carcinoma Primary squamous cell carcinoma	Mucoepidermoid carcinoma Adenoid cystic carcinoma Adenocarcinoma, NOS intraductal Carcinoma Carcinoma-ex Pleomorphic adenoma

MILAN SYSTEM FOR CLASSIFICATION OF SALIVARY GLAND LESIONS			
CATEGORY	**FINDINGS**	**RISK OF MALIGNANCY**	**CLINICAL MANAGEMENT**
1. Non-diagnostic	Non-mucinous cyst fluid, non-neoplastic acinar cells, poorly prepared slides	25%	Clinical and radiologic correlation/repeat FNA
2. Non-Neoplastic	Inflammatory/reactive changes (e.g., reactive lymph node, infection)	10%	Clinical follow-up and radiologic correlation
3. Atypia of Undetermined Significance	Indefinite for neoplasm (often inadequately sampled neoplasm)	20%	FNA or Surgery
4A. Neoplasm: Benign	E.g., Pleomorphic adenoma, Warthin Tumor	<5%	Surgery or follow up
4B. Salivary gland Neoplasm of Uncertain Malignant Potential (SUMP)	Basaloid neoplasm, oncocytic/squamoid subtype, monomorphic basaloid, cellular basaloid neoplasms	35%	Surgery
5. Suspicious for Malignancy	Features suspicious for malignancy but not unequivocal	60%	Surgery
6. Malignant	Clearly malignant(, etc…). Try to subtype and grade if possible	90%	Surgery

12. HEAD AND NECK PATHOLOGY

OCULAR PATHOLOGY



CHRONIC CONJUNCTIVITIS

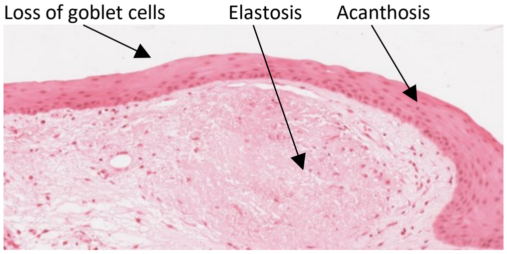
MORPHOLOGY

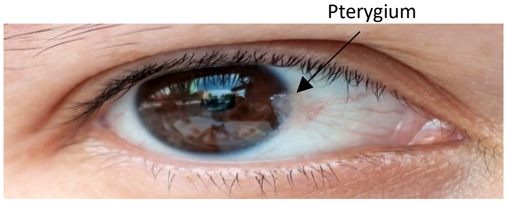
- **Papillary squamous epithelium** with **goblet cell hyperplasia** and **hypertrophy**
- Prominent **plasmacytic infiltrate** with normal **background lymphocytes**
- Scattered **lymphoid follicles**
- May have **retention cysts**
- Late changes include **keratinization**, **scarring**, and **atrophy of epithelium**

OTHER HIGH YIELD POINTS

- Classified as either a **chronic follicular conjunctivitis** or **chronic papillary conjunctivitis**
- Can caused by **infectious agents** (EBV, Adenovirus, Poxviridae, Moraxella spp., Chlamydia psittaci, Mycobacteria Tuberculosis), cosmetic agents, medications, vitamin A deficiency, or allergies
- **Molecular testing** for **Chlamydia psittaci** is gold standard
- May be **unilateral** or **bilateral**

Path Presenter





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PTERYGIUM

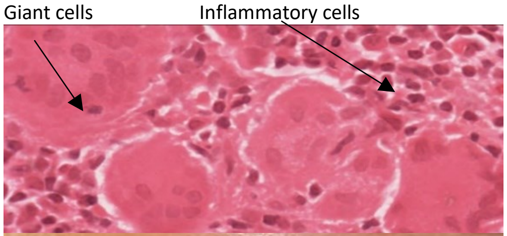
MORPHOLOGY

- **Epithelial changes**: **loss of goblet cells**, **squamous acanthosis**, and **atrophy**
- **Dissection of Bowman layer** from the fibrovascular connective tissue
- Fibrovascular tissue has **elastosis** in addition to the vascular and connective tissue components
- **Variable** acute and chronic **inflammation**

OTHER HIGH YIELD POINTS

- Seen in individuals who have **prolonged sun or UV exposure**
- UV exposure is the **most important risk factor**
- **May recur** in approximately 20% of individuals even after surgical management

Path Presenter



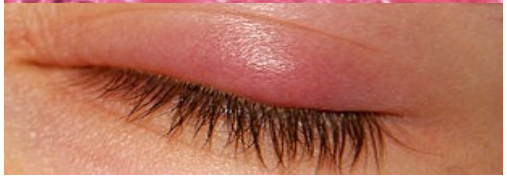


Image credits: JD on Wikimedia

CHALAZION

MORPHOLOGY

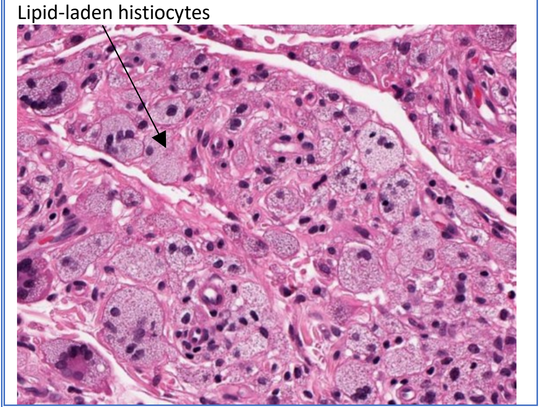
- Epithelioid and **foamy histiocytes** and **multinucleated giant cell granulomas** surrounding "empty" spaces nonstaining lipid ("**lipogranuloma**")
- Abundant **acute inflammation** with **neutrophilic predominance**
- **Asteroidal bodies** and **conchoid bodies** may be present

OTHER HIGH YIELD POINTS

- Most often occurs on the **upper eyelid** but can be seen in lower eyelid
- This is a **non-tender**, **solitary nodule** that is **slow growing**
- Hypothesized to be due to inflammation of surrounding **sebaceous glands** that **become obstructed**
- If it **ruptures past the tarsal conjunctiva**, may cause **pyogenic granuloma**

Path Presenter

12. HEAD AND NECK PATHOLOGY



XANTHELASMA

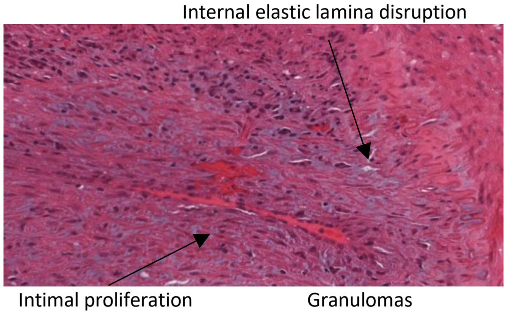
MORPHOLOGY

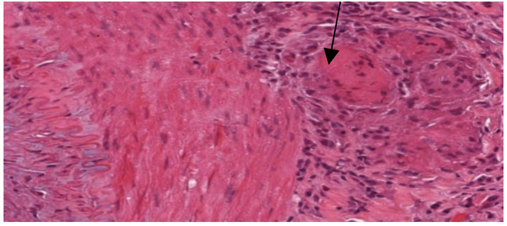
- **Dermal based** collection of **lipid-laden histiocytes**

OTHER HIGH YIELD POINTS

- Presents as a **small yellow plaque** on the **medial eyelid**
- May be seen in **younger individuals if** there is a **history of familial hypercholesterolemia**
- **Plaques often recur** and have a higher recurrence if familial hypercholesterolemia is present

Path Presenter





GIANT CELL ARTERITIS

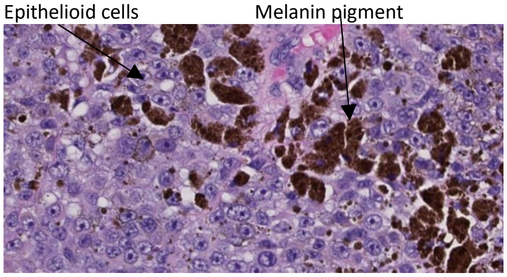
MORPHOLOGY

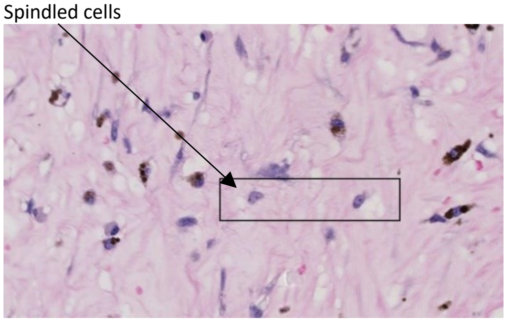
- **Transmural necrotizing inflammation** composed of **acute** and **chronic inflammatory cells** and **granulomas** which **surrounding artery**
- **Intimal proliferation** and **disrupted internal elastic lamina**
- **Arteriosclerosis** and or **vascular obliteration** is seen in long-term if untreated

OTHER HIGH YIELD POINTS

- Most commonly is a **lesion which requires a large sampling** as **lesions are often discontinuous**
- Patients often present with **fevers**, **vision changes/loss in ipsilateral eye** of affected vessel, and **malaise**
- Can be **isolated** to a **single vessel or multisystem** involvement
- **Special stains**: **Trichrome-elastic**, or **elastic stain** are useful
- **Responds** well **to steroids** +/- methotrexate
- Associated with **polymyalgia rheumatica**

Path Presenter





UVEAL MELANOMA

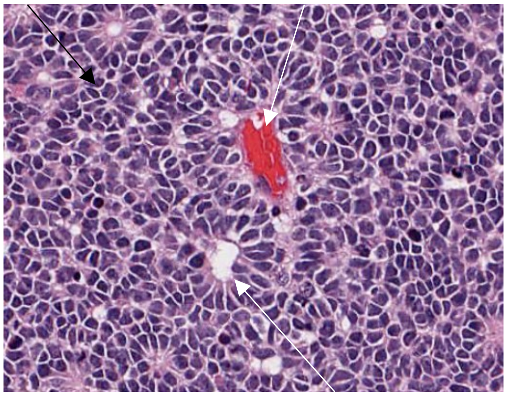
MORPHOLOGY

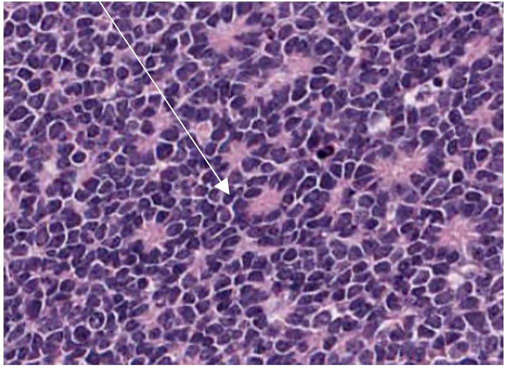
- Presents as either **spindle cell variant** or **epithelioid variant:**
    - **Spindle cell variant:** melanocytes have elongated ovoid nuclei, conspicuous nucleoli, and variable indistinct eosinophilic cytoplasm
    - **Epithelioid variant:** polygonal melanocytes with atypical nuclei, conspicuous nucleoli, and occasional nuclear pseudoinclusions, and variable pale to eosinophilic cytoplasm
- **May or may not have** melanin **pigment**

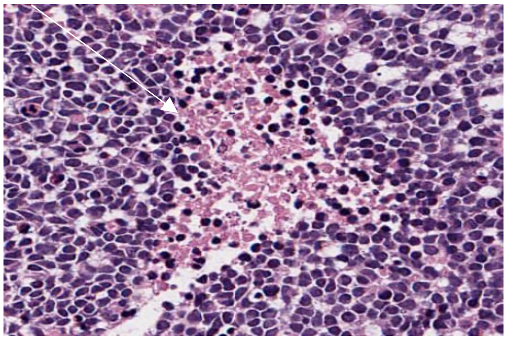
OTHER HIGH YIELD POINTS

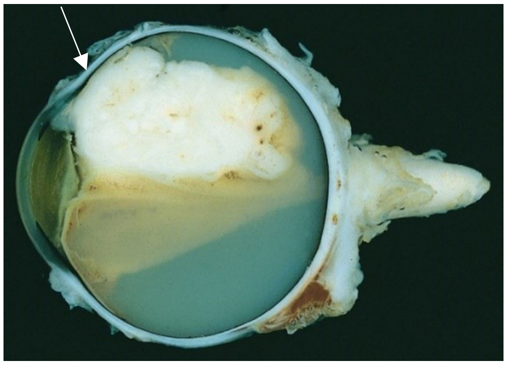
- Usually seen in **elderly males** and nearly **half of all cases** are **asymptomatic**
- **Metastasis seen in about half** of cases and nearly **all are liver metastases**
- **Prognostic factors**: include size, extraorbital extension, metastasis, recurrence, and cytogenetic abnormalities (monosomy 3, and +8q), tumor infiltrating lymphocytes, and matrix loops
- **IHC**: Positive for HMB45, S100, MelanA/MART1, MITF, SOX-10
- **Molecular**: GNAQ or GNA11 mutations; may have BAP1, EIF1AX, SF3B1

Path Presenter


Blue cells
Pseudorosette


Homer-Wright rosette
Flexner-Wintersteiner Rosette




Retinoblastoma

Provided by: Armed Forces Institute of Pathology

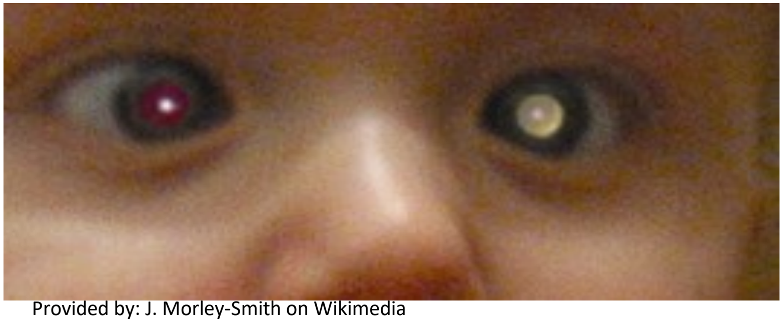
RETINOBLASTOMA

MORPHOLOGY

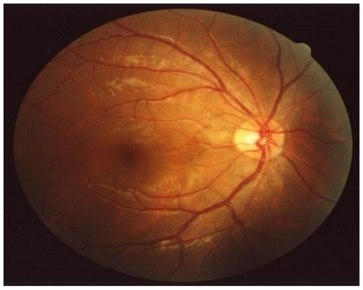
- Small **blue cell tumor** with **scant cytoplasm**
- Arranged in **trabecular**, **nests**, and **sheets**, and may have **rosette formation**
- Rosettes can be with a **central lumen** (**Flexner-Wintersteiner**) or **without a central lumen** (**Homer-Wright**), or a **pseudorosette** (surrounding vessel)
- Can see **calcifications** and **necrosis** from ischemia
- **Fleur de lis** is a **group of Flexner-Weinsteiner rosettes** side by side

OTHER HIGH YIELD POINTS

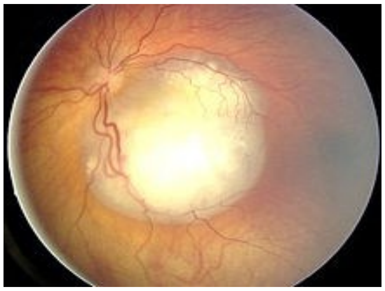
- **Most common childhood intraocular malignancy** and **more than 90% occur** in **middle** and **low-income countries**
- Presents with **leukocoria**, **strabismus**, **glaucoma**, **retinal detachment**, and **decreased acuity**
- Can have an **endophytic** or **exophytic growth** pattern
- **Prognosis** is largely **dependent** on **socioeconomic status**
- **High risk features** include **involvement of choroid**, **anterior structures**, and **optic nerve**
- **IHC**: Positive for **synaptophysin**, **NSE**, **Rb**, and **SOX2**; **negative** for **CD99**, **GFAP**, and leukocyte markers
- Occurs due to the **Knudson "Two-Hit" hypothesis** in which the **first mutation** is in either **somatic or germ-line** and the **second mutation is** in **somatic** cells
- **Molecular**: **Inactivation** or **loss of function** of the tumor suppressor **RB1** on **chromosome 13q**
  - Other mutations include **BCOR**, **MYCN** (in non-RB1 cases), and chromosomal abnormalities in 1q, 1p, 6p, and 16 (monosomy


Normal Eye
Leukocoria in affected eye

Provided by: J. Morley-Smith on Wikimedia


Normal Eye on Fundoscopy

Provided by: Ignis on Wikimedia


Retinoblastoma on Fundoscopy

Provided by: I Aerts on Wikimedia

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Corpora Amylacea. Image courtesy: Ziad El-Zaatari, MD

CHAPTER 13: MALE GENITAL PATHOLOGY

Devi Jayachandran, MD
Snehal Sonawane, MD
Akanksha Gupta, MD

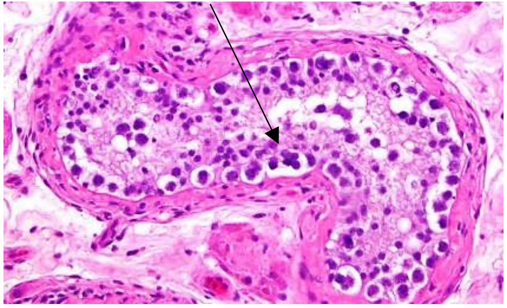
13. MALE GENITAL PATHOLOGY

TESTIS

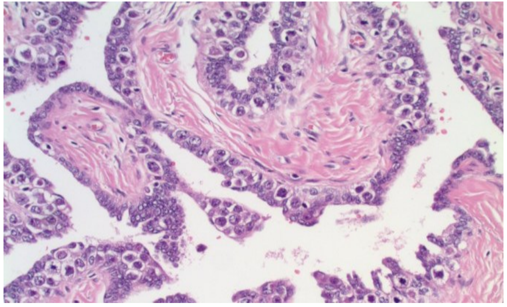
GERM CELL TUMORS (GCT)

GERM CELL TUMORS RELATED TO GERM CELL NEOPLASIA IN SITU

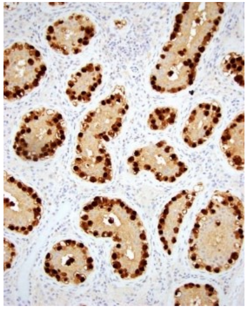
Malignant germ cells in GCNIS (fried egg)



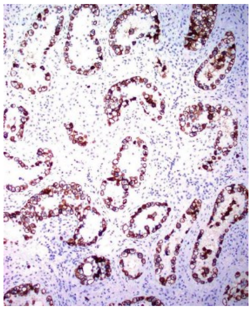
GCNIS: Pagetoid extension into the rete testis



Credit: Ankur Sangoi, MD @slusagar



OCT 3/4



CD117

GERM CELL NEOPLASIA IN SITU (GCNIS)

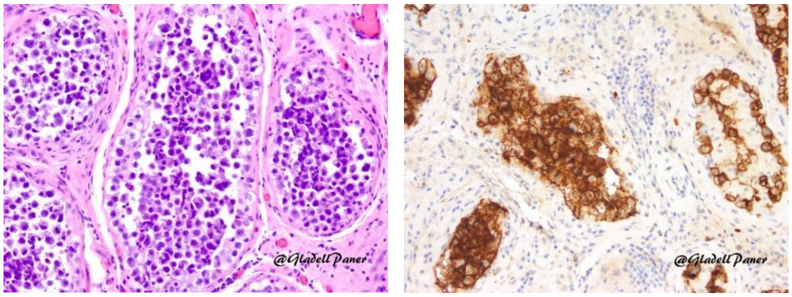
MORPHOLOGY

- **Precursor lesion**: ~50% progresses to malignant Germ Cell Tumor within 5yrs.
- Associated with cryptorchid testis
- **Proliferation of atypical germ cells within seminiferous tubules**
- Large, angulated nuclei with coarse chromatin with prominent halos (resemble fried egg)
- Often located at base of tubules
- Often **associated with adjacent malignant germ cell tumors**.
- Can show pagetoid extension into the rete testis
- Often absent spermatogenesis.
- **Identical IHC profile to seminoma: OCT3/4, cKit (+)**

OTHER HIGH YIELD POINTS

INTRATUBULAR SEMINOMA

- **Complete filling of expanded seminiferous tubule by neoplastic cells**
- Intermediate stage between GCNIS and Invasion
- Unlike GCNIS, Sertoli cells are usually not present in the involved seminiferous tubules



H and E: intratubular seminoma, IHC: CD117 positive in intratubular seminoma and GCNIS
Credit: Gladell Paner, MD @GladellPaner

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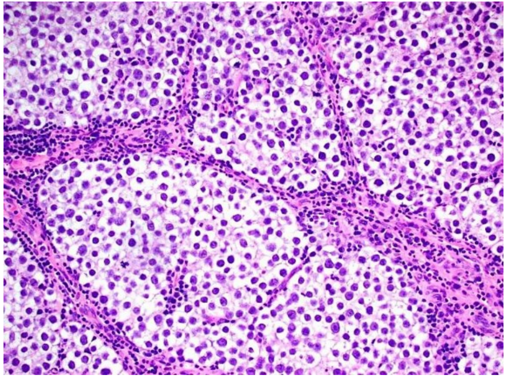
Nested polygonal cells, clear cytoplasm, fibrous septae with lymphocytic infiltrate



Striped/ Tigroid appearance on smear in Seminoma

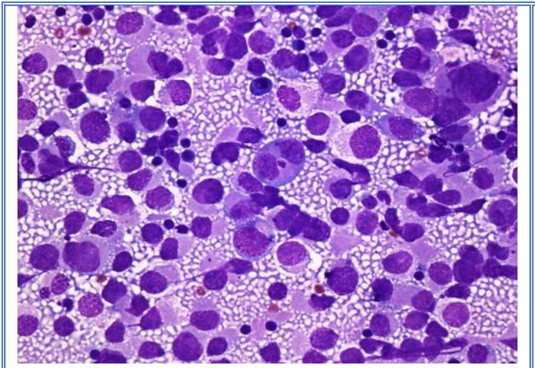
SEMINOMA

MORPHOLOGY

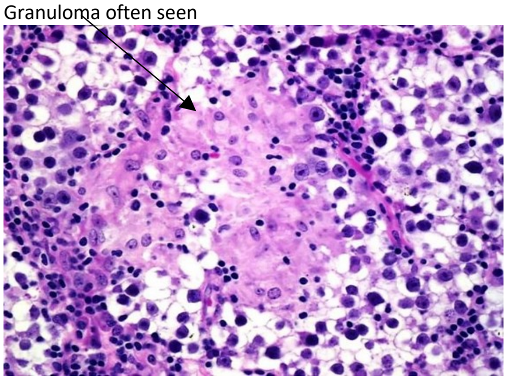
- **Most common germ cell tumor** (~50%).
- Often present as unilateral mass.
- **Well circumscribed solid, fleshy, tan lobulated lesion**
- **Large nested polygonal cells with clear to eosinophilic cytoplasm** (full of glycogen), distinct cell membranes, vesicular chromatin, and prominent nucleoli
- Tumor nests, separated by fibrous septae with lymphocytic infiltrate
- Often adjacent GCNIS in residual tubules
- Rare syncytiotrophoblasts and granuloma can be seen
- **IHC: (+) OCT3/4, CD117, D2-40, SALL4, elevated serum LDH, rarely hCG**

OTHER HIGH YIELD POINTS

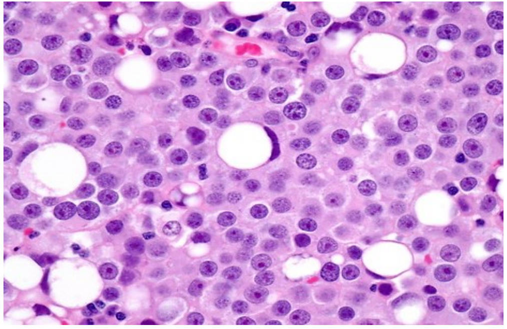
- Metastases often to retroperitoneal lymph nodes



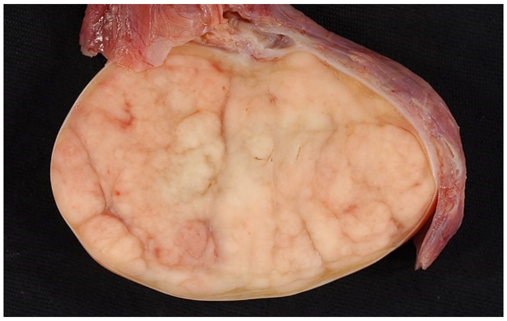
Granuloma often seen



Rarely Signet ring-like cell can be seen



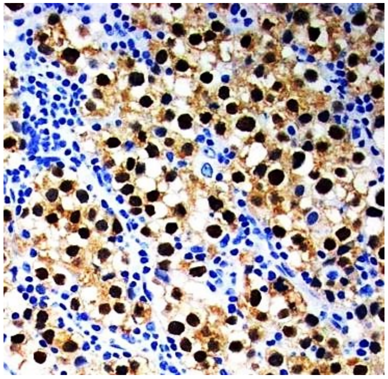
Seminoma gross appearance; Credit: Wikimedia Commons



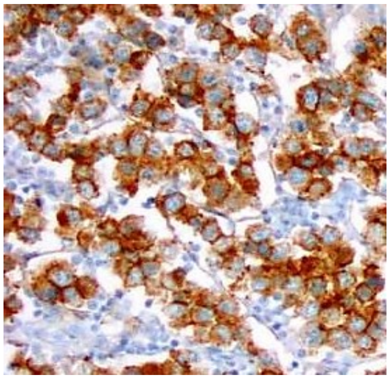
[Path Presenter](#)

- Molecular: majority have **isochromosome 12p; c-kit mutations**
- **Prognosis: Good if treated, chemo sensitive**

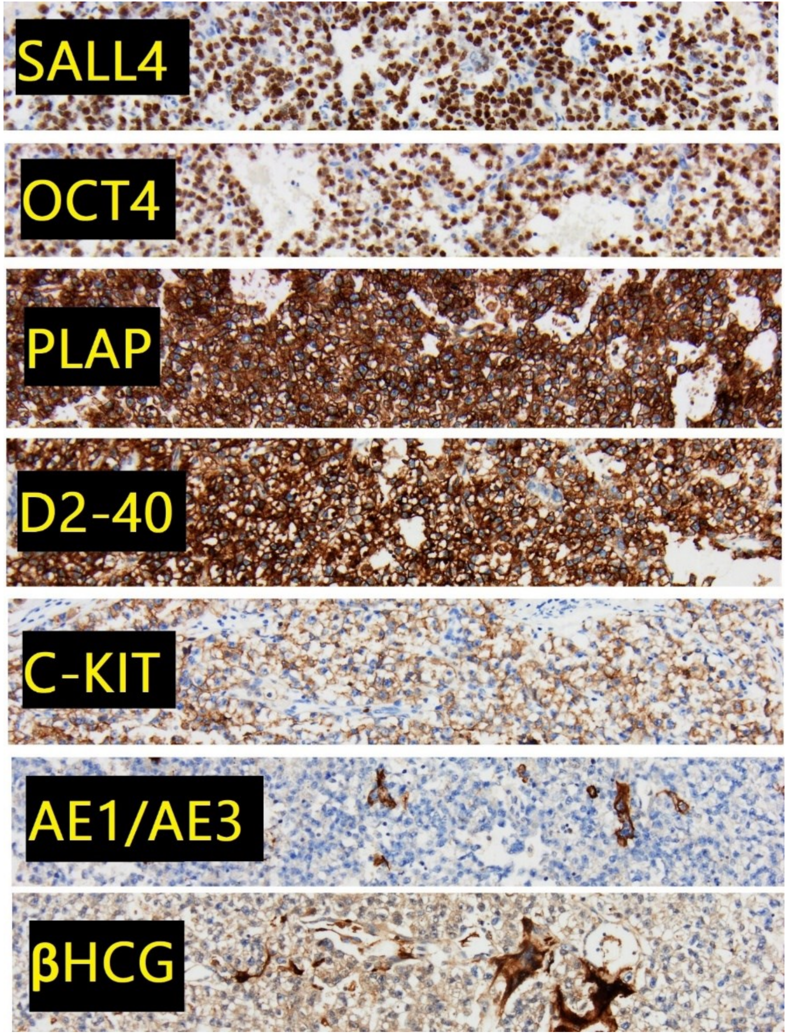
OCT 3/4 Positive



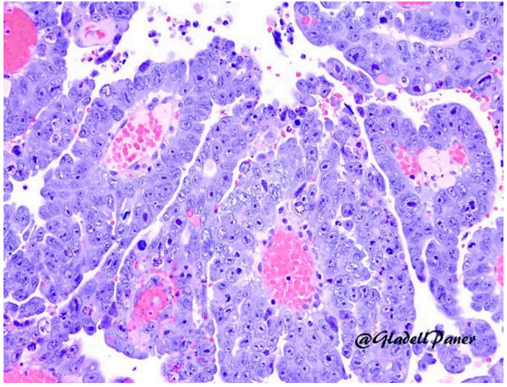
CD117 Positive



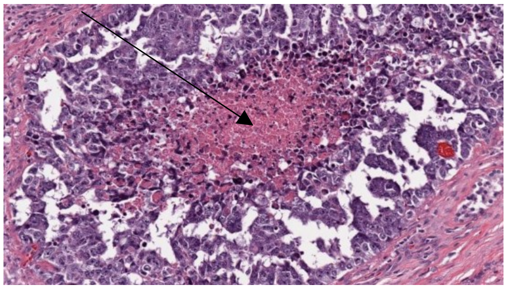
Seminoma IHC (credit: Beatriz Agredano, MD, Spain)



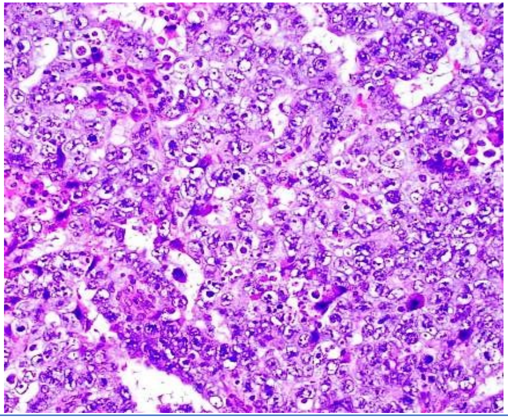
Embryonal carcinoma



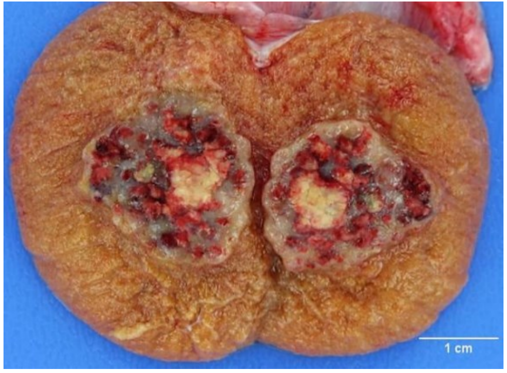
Necrosis



Prominent nucleoli, mitosis, apoptosis



Variegated appearance with hemorrhage and necrosis



EMBRYONAL CARCINOMA

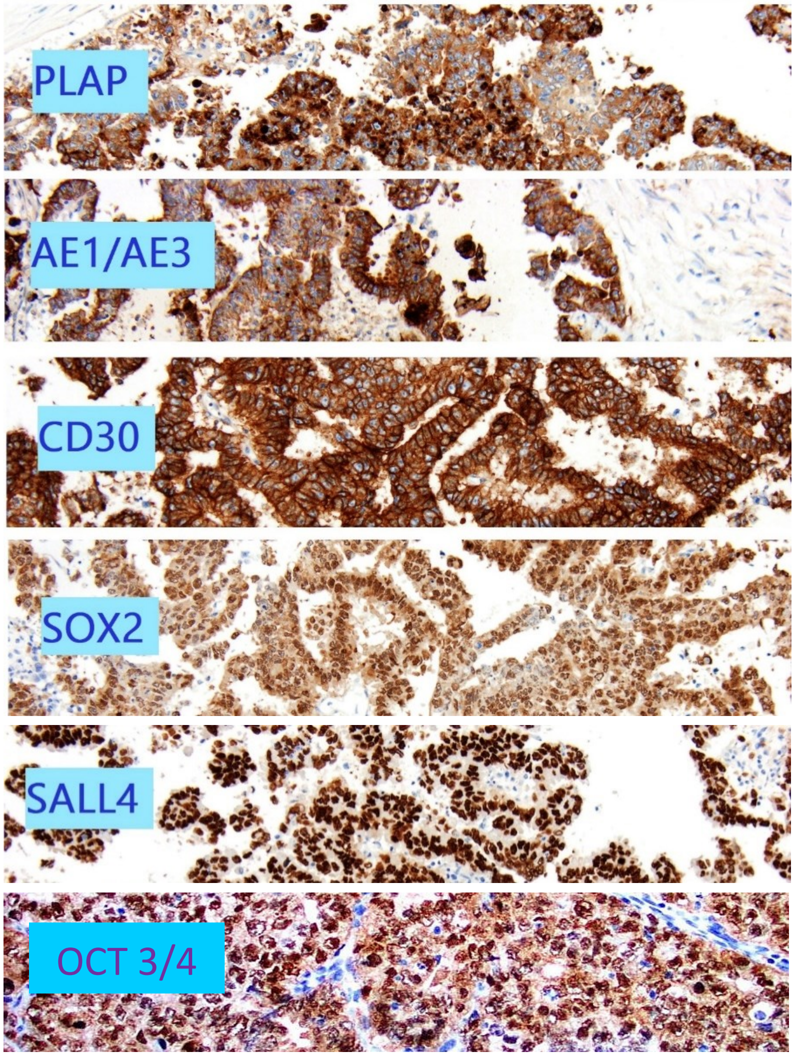
MORPHOLOGY

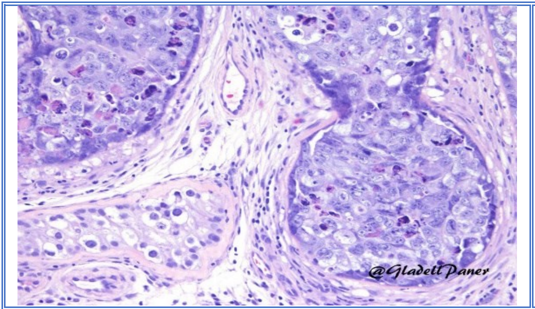
- **Second-most common testicular GCT**, u**sually part of a mixed GCT**
- Composed of rudimentary cells with epithelial differentiation and marked **cytologic** atypia
- Variety of growth patterns (nests, sheets, papillae, glands)
- Large, crowded, **"Primitive" pleomorphic cells** with vesicular nuclei, basophilic chromatin, prominent nucleoli and amphophilic cytoplasm
- **Prominent mitoses and apoptotic bodies** are present
- **Frequent hemorrhage and tumor necrosis**
- Intratubula**r** EC with comedonecrosis and coarse calcification
- **IHC: Positive for CD30, OCT3/4, AE1/AE3, SALL4**

OTHER HIGH YIELD POINTS

- Molecular: **Isochromosome 12p amplification**
- Prognosis: **Aggressive**, but often **responds to chemotherapy**

Embryonal carcinoma IHC (credit: Beatriz Agredano, MD, Spain)





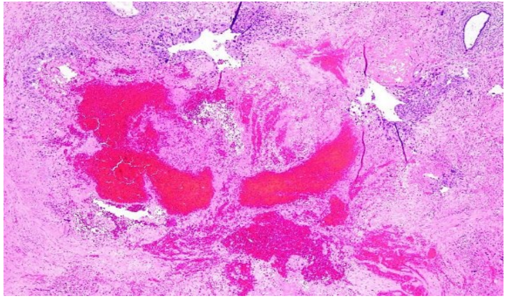
INTRATUBULAR EMBRYONAL CARCINOMA (ITEC)

- **Complete filling of expanded seminiferous tubule by neoplastic cells**
- Precursor lesion of non - seminomatous tumor

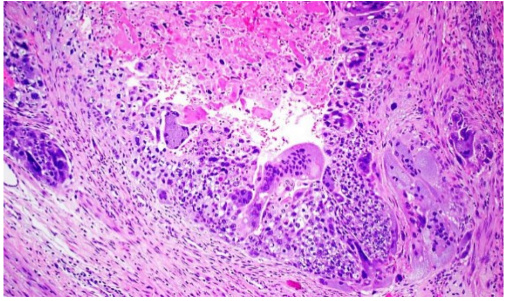
Figure: Intratubular Embryonal carcinoma with adjacent GCNIS
Credit: Gladell Paner, MD

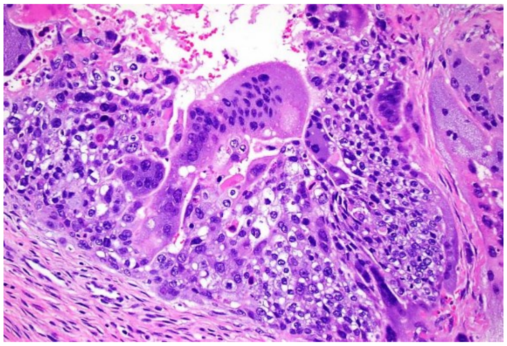
Path Presenter

Extensive hemorrhage and necrosis

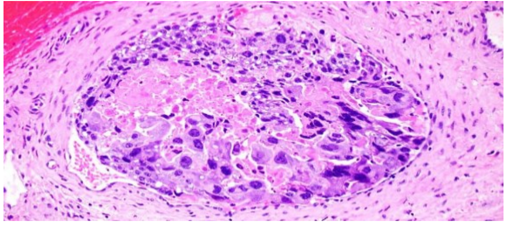


Viable tumor at the periphery





Lymphovascular invasion



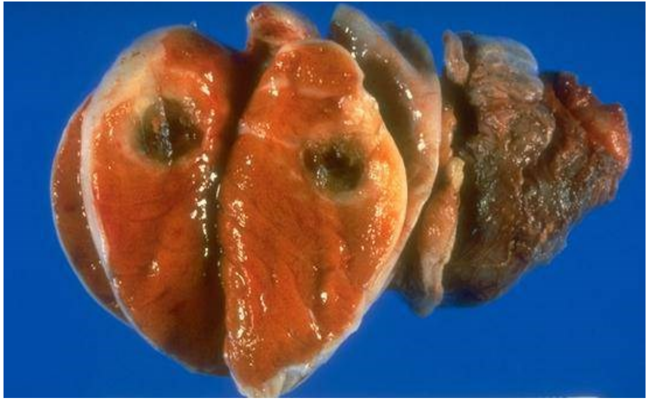
CHORIOCARCINOMA

MORPHOLOGY

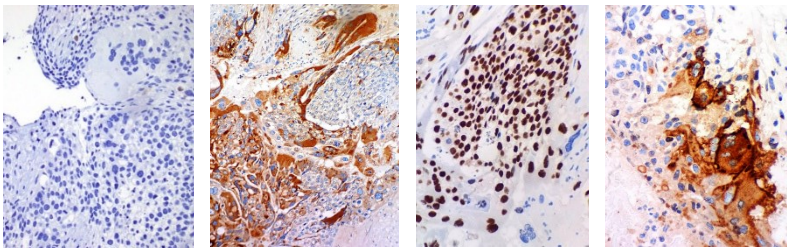
- Usually**, a part of a mixed GCT**
- **Extensive hemorrhage and necrosis** with little viable tumor at the periphery
- Tumor is composed of mixture of **Syncytiotrophoblasts giant cells** and mononuclear trophoblastic cells (**cytotrophoblasts**) and intermediate trophoblasts.
- **Lymphovascular invasion** and blood vessel invasion is very common
- STGC have numerous hyperchromatic nuclei and **abundant cytoplasm** with distinct **cytoplasmic vacuoles**
- **Smaller cells** are the **cytotrophoblasts** and intermediate trophoblastic cells with distinct cell borders, pale cytoplasm, mildly pleomorphic nuclei, and prominent nucleoli, they **form tight clusters**
- IHC**: Positive hCG, Syncytiotrophoblasts: Positive for inhibin, glypican-3**
- **Cytotrophoblasts: Positive for SALL4, p63, GATA3**
- Elevated Serum hCG

OTHER HIGH YIELD POINTS

- Most aggressive GCT, less responsive to treatment
- Frequent early hemorrhagic metastases to lung

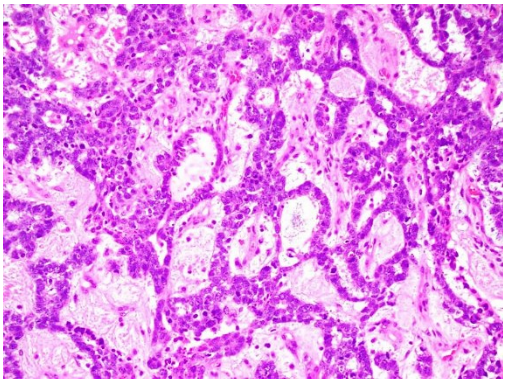


Path presenter

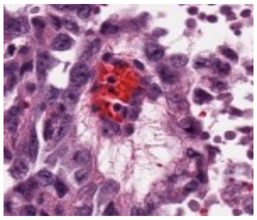


OCT 3/4, B-HCG, GATA3 and Glypican stains.

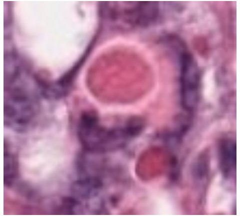
Yolk Sac tumor



Schiller-Duval Bodies



Hyaline globules



Path Presenter

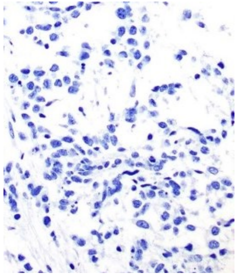
YOLK SAC TUMOR, POSTPUBERTAL-TYPE/ ENDODERMAL SINUS TUMOR

MORPHOLOGY

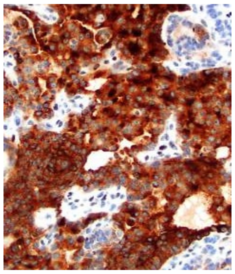
- Almost always a **component of mixed GCT**
- Many patterns/architecture (often combined)
- Growth patterns **recapitulate yolk sac, allantois, and extraembryonic mesenchyme**
- Most common pattern reticular/microcystic (Honeycomb meshwork)
- Can also be solid, papillary, glandular, etc
- Often hypocellular myxoid areas are present
- **Schiller-Duval Bodies**, refractile **eosinophilic hyaline globules** and band-like intercellular basement membrane material are helpful clues
- **IHC: Positive for AFP, Glypican-3, SALL4, AE1/AE3**

OTHER HIGH YIELD POINTS

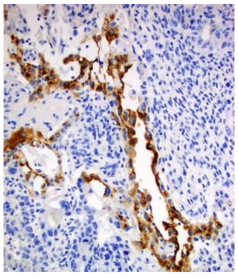
- **Elevated Serum AFP**
- Common in Post-chemo cases (sarcomatoid YST)
- Can have **"hepatoid"** areas resembling liver that stains with liver markers



OCT3/4

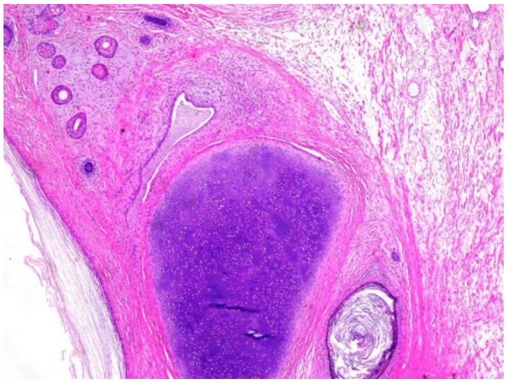


Glypican

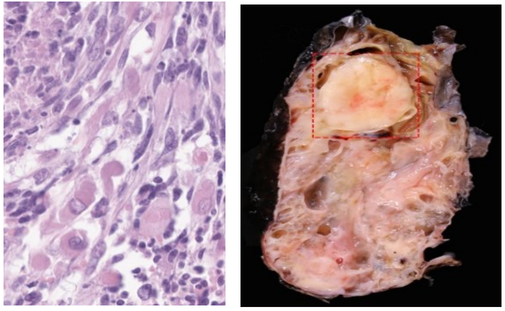


AFP

Teratoma



Rhabdomyosarcoma in a teratoma



Credit: Andres Martin Acosta MD @Andres_M_Acosta

TERATOMA, PREPUBERTAL-TYPE

MORPHOLOGY

- **Most common component in a treated GCT**
- Composed of **tissues from one or more germinal layers**
- May be composed of **mature and /or immature, embryonic-type tissue**
- Often part of a mixed GCT
- Composed of **multiple cysts lined by glandular or squamous epithelium**
- Often areas of cytologic atypia, including primitive mitotically active stroma cuffing glands are present
- Frequent immature neuroectodermal structures can be seen

SOMATIC-TYPE MALIGNANCY ARISING IN A TERATOMA

- **If a dysplastic component forms a nodule that is larger than a 4X field (5 mm)**
- Usually a sarcoma, **most commonly rhabdomyosarcoma**
- Most common carcinoma is adenocarcinoma of various growth patterns

OTHER HIGH YIELD POINTS

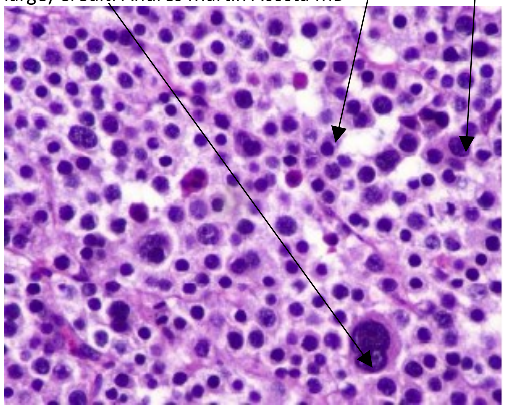
- Unlike ovary, **all teratomas in post pubertal testis are malignant**!
- Rare situation benign teratoma can occur in an adult: Dermoid cysts, or prominent components of ciliated epithelium and smooth muscle
- However, **no GCNIS, isochrome 12p, or testicular scarring should be noted**

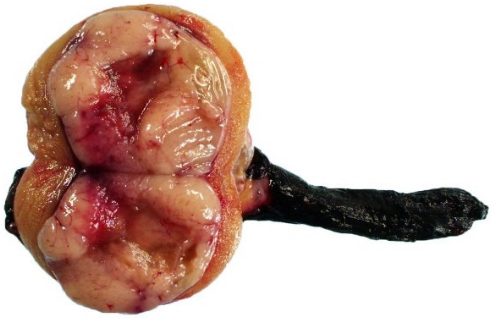
Path Presenter

13. MALE GENITAL PATHOLOGY

GERM CELL TUMORS UNRELATED TO GERM CELL NEOPLASIA IN SITU

Spermatocytic tumor (3 cell types: small, medium & large) Credit: Andres Martin Acosta MD





Credit: Phoenix Bell MD @PhoenixBellMD

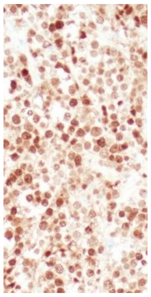
SPERMATOCYTIC TUMOR

MORPHOLOGY

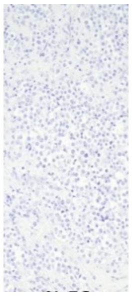
- Relatively **rare**
- Usually occurs in older men (>50yo)
- **NOT associated with GCNIS or cryptorchidism**
- Polymorphous cell population (**3 cell types: small, medium, and large**)
- Tumor cells with poorly defined cell membranes, dense cytoplasm,
- **Round nuclei with dense to granular chromatin**
- Diffuse to multinodular pattern of growth.
- Frequent cystic change/edema are present
- No significant inflammation/granulomas are seen
- **IHC: Negative for usual seminoma markers, + SALL 4, CD117 (50%), SSX**
- Can undergo sarcomatous transformation

OTHER HIGH YIELD POINTS

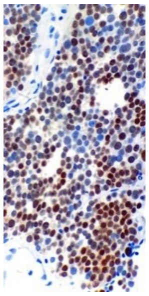
- **Excellent prognosis**
- NOT a component of mixed GCT



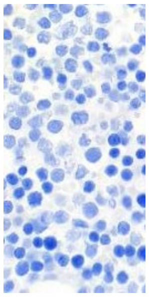
SSX



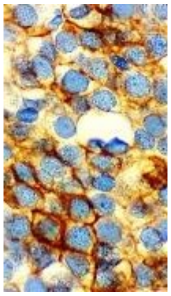
D2-40



SALL4

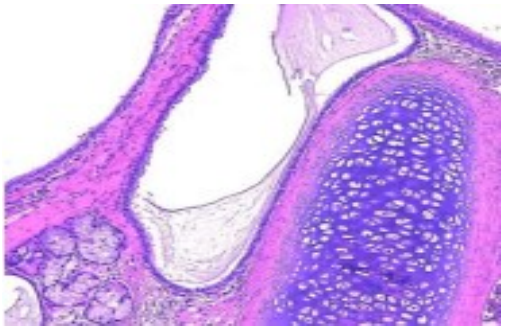


OCT3/4

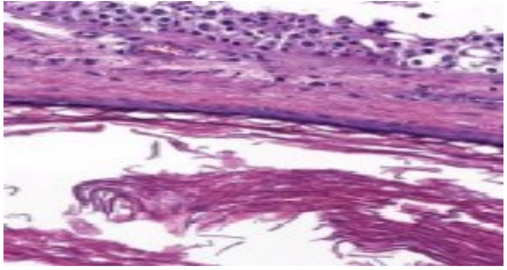


CD117

Teratoma



Epidermoid cyst



TERATOMA, PREPUBERTAL-TYPE

MORPHOLOGY

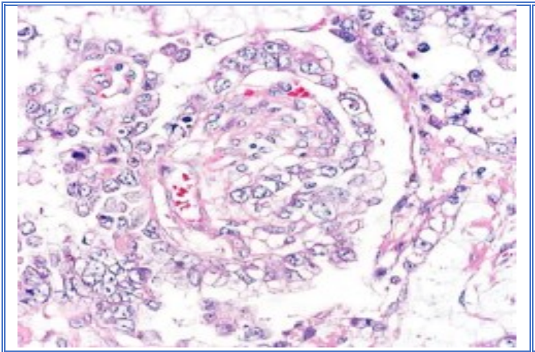
- Composed of tissues from **one or more germ cell layers**
- Primarily occurs in **prepubertal males <6 years old**
- Frequently include **skin structures, ciliated epithelium, fat, cartilage, bone, and muscle** in organoid structures

SPECIALIZED VARIANTS:

- **Dermoid Cyst: replicate skin**
- Squamous epithelium with adnexal structures
- **Epidermoid Cyst**: Unilocular cyst with **squamous lining** and keratinaceous debris. No adnexal structures or other elements
- **Well-differentiated Neuroendocrine Tumor**: Similar morphology to elsewhere. Often pure. Usually good behavior, can behave aggressively

OTHER HIGH YIELD POINTS

- Unlike Post pubertal type: **Benign behavior**, do not recur or metastasize
- **NO association with GCNIS, tubular atrophy, scar or isochrome 12p amplification**
- **NO association with mixed GCT**
- Like mature cystic teratomas seen in the ovary



YOLK SAC TUMOR, PREPUBERTAL-TYPE

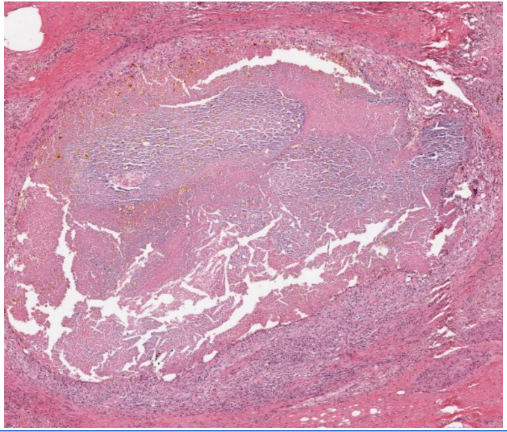
MORPHOLOGY

- Identical morphology and IHC profile to post pubertal type
- **Secretes AFP**

OTHER HIGH YIELD POINTS

- Rare
- Usually in young boys <6 years old
- Usually pure, but can see in combination
- Unlike post pubertal YST: **NOT associated with GCNIS or isochrome 12p amplification**
- **Excellent survival**, even with advanced stage

Regressed Seminoma



REGRESSED GERM CELL TUMORS

MORPHOLOGY

- Well-delineated nodular focus of **scaring fibrosis in the testis**
- Germ cell tumors that have undergone either partial or complete regression ("burnt-out")
- **Can present with metastatic disease**, even after complete regression of primary tumor
- Can be seminoma or non-seminomatous.
- **Coarse calcifications within tubules, chronic inflammation, hyalinized tubular ghosts cells can be seen**
- GCNIS, tubular atrophy, microliths may also seen

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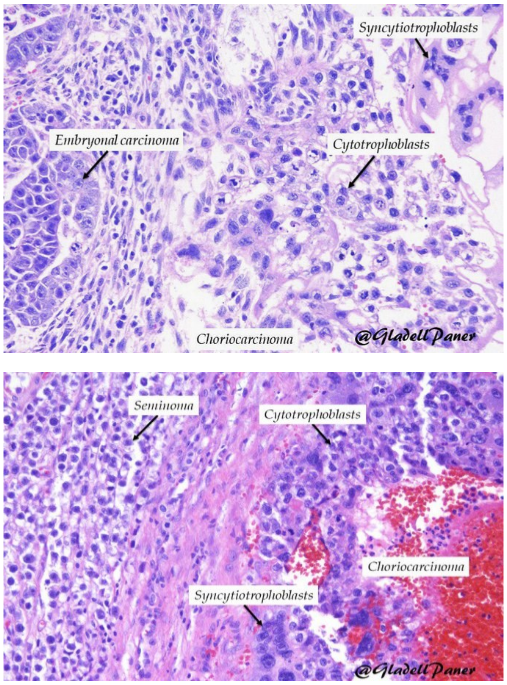

Syncytiotrophoblasts
Embryonal carcinoma
Cytotrophoblasts
Choriocarcinoma
@GladellPaner
Seminoma
Cytotrophoblasts
Choriocarcinoma
Syncytiotrophoblasts
@GladellPaner

Mixed Germ Cell Tumor

MIXED GERM CELL TUMOR

MORPHOLOGY

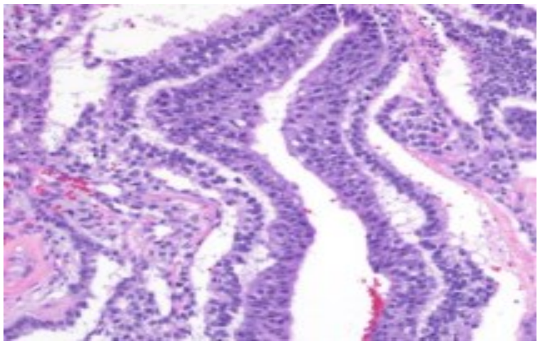
- **Malignant tumors with more than one germ cell tumor component**
- Clinically regarded as "non-seminoma" (even if seminoma present)
- Majority of all non-seminomatous GCT are mixed
- **Must report approximate % of each component**

OTHER HIGH YIELD POINTS

- Syncytiotrophoblasts ≠ choriocarcinoma (can see in other tumors, like seminoma)

SPECIAL SUBTYPES:

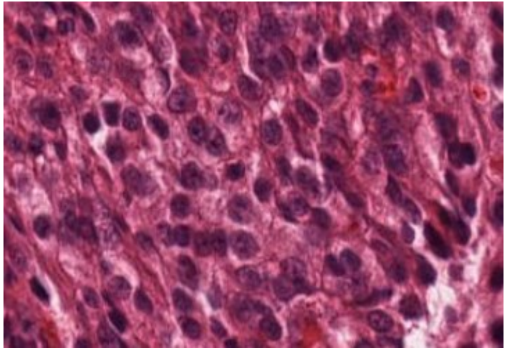
- **Polyembryoma:** Embryonal carcinoma and **YST resembling an embryo**
- **Diffuse embryoma:** Embryonal carcinoma and **YST in parallel flat layers**



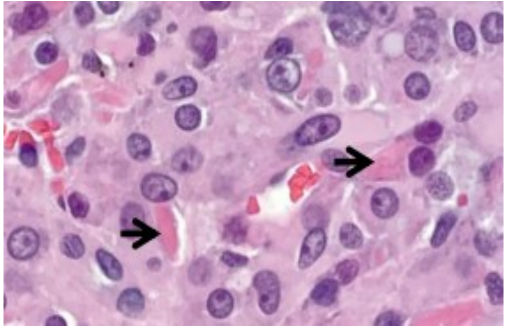
Diffuse embryoma

SEX-CORD-STROMAL TUMORS

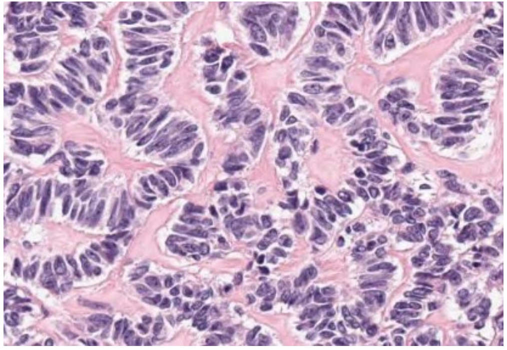
Round cells, eosinophilic granular cytoplasm



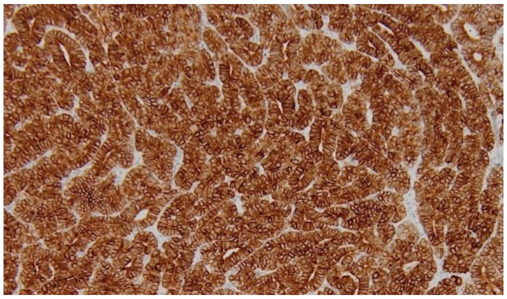
Reinke crystals



Tubular-glandular growth pattern



Inhibin



Path Presenter

[PP link](#) [PP link](#)

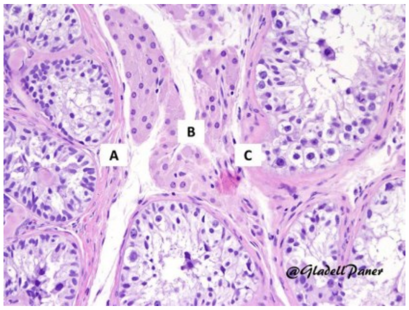
LEYDIG CELL TUMOR

MORPHOLOGY

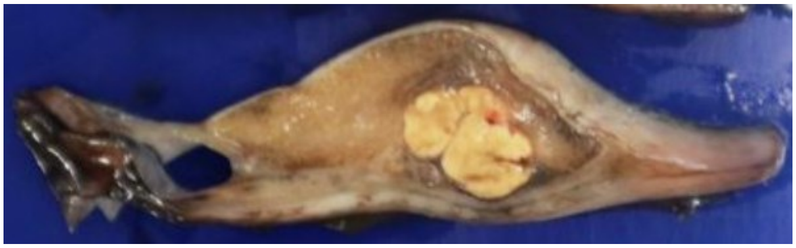
- Vast majorities are **benign**, (**5-10% are malignant**)
- **Most** common **sex cord-stromal tumor in testis**
- Any age with 2 peaks: **5-10 and 30-60 years**
- Usually asymptomatic, but can present with precocious puberty
- **Well-circumscribed, intraparenchymal nodule** with golden-brown homogeneous cut surface
- Diffuse growth of uniform round cells with round central nuclei, prominent nucleoli and abundant, eosinophilic granular or vacuolated cytoplasm
- Frequent **Reinke crystals** (30-40%) can be seen
- Focal nuclear pleomorphism, binucleation or multinucleation may be seen
- IHC: **Positive for inhibin-α, calretinin, Melan-A (MART-1), SF1, CD99, and vimentin (strong and diffuse)**
- **Negative for cytokeratins**

OTHER HIGH YIELD POINTS

- Metastasis is only criterion for malignancy
- **Leydig hyperplasia is the major differential (less than 0.5 cm)**



A - Sertoli cell nodule (Pick's adenoma)
B - Leydig cell hyperplasia
C - Germ cell neoplasia in situ (GCNIS)
Credit: Gladell Paner, @GladellPaner



Credit: Varsha Manucha, MD @VarshaManuchaMD

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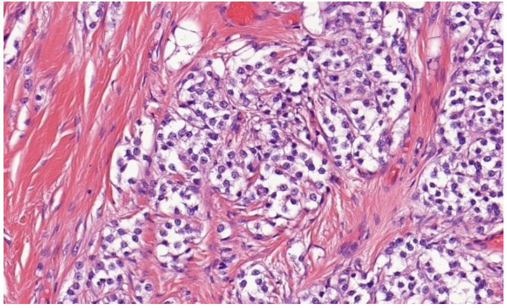
SERTOLI CELL TUMOR

MORPHOLOGY

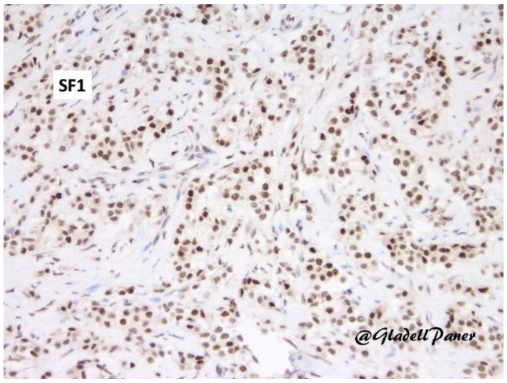
- **Pure sex cord-stromal tumor composed of Sertoli cells only**
- **Small, firm, well-circumscribed, intraparenchymal nodule with grey-white homogeneous cut surface**
- Growth pattern: Tubular-glandular or solid sheets, rarely spindle cell pattern
- Cuboidal or columnar cells with moderate pale to lightly eosinophilic cytoplasm, often prominent cytoplasmic vacuoles

Sertoli cell tumor: Cell arranged in nests



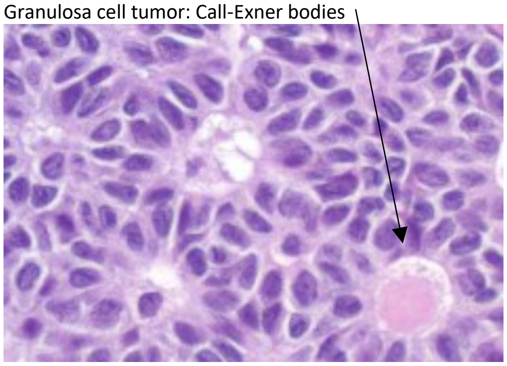
Credit: Tristan D Rutland MBBS FRCPA @TristanRutland7

SF1 IHC in Sertoli cell tumor

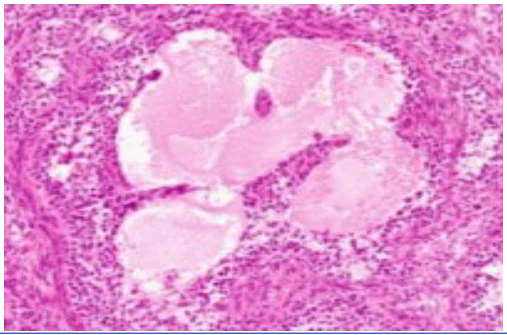


Credit: Gladell Paner, MD @GladellPaner

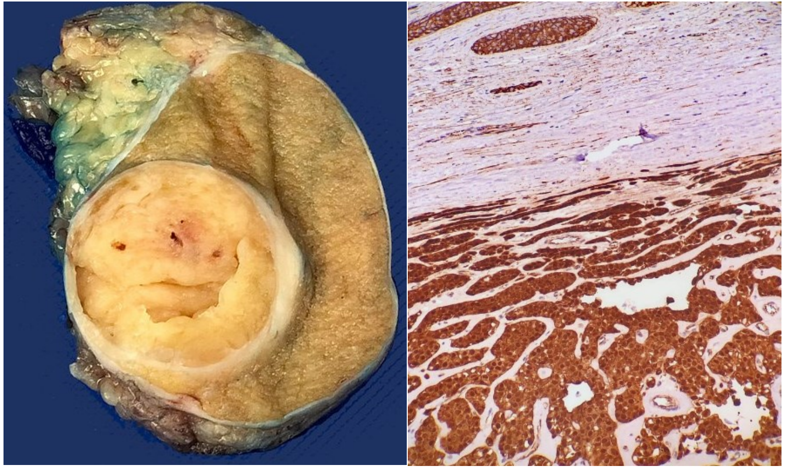
Granulosa cell tumor: Call-Exner bodies



Macrofollicles with mucinous secretions



- IHC: **Positive for inhibin-α, calretinin, Melan-A (MART-1), SF1, WT1, chromogranin, synaptophysin, AE1/AE3, nuclear β-catenin**
- **Sclerosing Sertoli Cell Tumor**—extensively hyalinized stroma with cells arranged in tight cords and clusters



Sertoli cell tumor shows nuclear (and cytoplasmic) β-catenin localization. The seminiferous tubules above show membranous staining
Credit: Daniel Levitan MD @levitan_daniel

OTHER HIGH YIELD POINTS

- Features of malignancy: **large size (> 5 cm), lymphovascular invasion, extra testicular extension, marked atypia , increased mitoses (> 5/10 HPF), and necrosis**
- Occur in patients with undescended testes, Peutz-Jegher's syndrome, Carney syndrome, androgen insensitivity, and testicular feminization syndromes

GRANULOSA CELL TUMOR

MORPHOLOGY

- Resembles ovarian counterpart
- Extremely rare in testis
- **Well-circumscribed, unencapsulated firm mass**

Adult Granulosa Cell Tumors:

- Varied architecture: **Sheet-like, trabecular, ribbon-like, microfollicular**
- **Pale cells with grooved nuclei**
- **Frequent Call-Exner bodies filled with pink secretions**
- **Frequent FOXL2 point mutations**

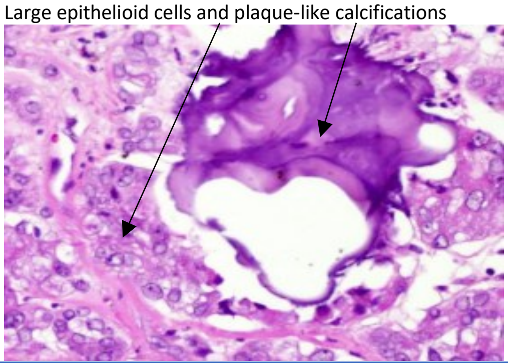
Juvenile Granulosa Cell Tumors:

- Rare, **almost all in first decade**, often before 6 months old
- Multiple irregular cystic areas filled with basophilic to eosinophilic secretion and interspersed solid areas
- Macrofollicles with mucinous secretions
- Round **nuclei with NO GROOVES**

OTHER HIGH YIELD POINTS

- Features of **aggressive behavior: Large size (> 4 cm), infiltrative borders frequent mitoses (> 5/10 HPF), lymphovascular invasion**

Large epithelioid cells and plaque-like calcifications



LARGE CELL CALCIFYING SERTOLI CELL TUMOR

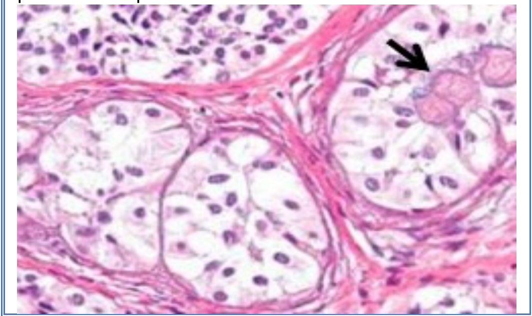
MORPHOLOGY

- **Extremely rare**
- Variant of Sertoli cell tumor with large epithelioid cells and **peculiar large, plaque-like calcifications**
- Often associated with **Carney complex**
- Often **prominent stromal neutrophilic infiltrate**
- **NO nuclear β-catenin**
- **IHC: Positive for SF1, inhibin, calretinin, S100, desmin, vimentin, EMA**

OTHER HIGH YIELD POINTS

- Frequently associated with **Carney complex**
- Frequent **PRKAR1A mutations**

Seminiferous tubules with large Sertoli cells and prominent deposits within tubules



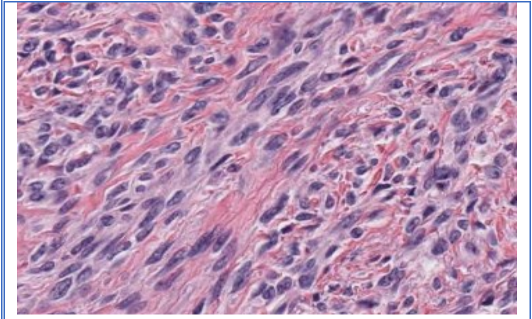
INTRA TUBULAR LARGE CELL CALCIFYING SERTOLI CELL TUMOR

MORPHOLOGY

- Often in **prepubertal males, present with gynecomastia**
- Bilateral
- Always **benign**
- Increased serum estradiol levels (aromatases made by tumor convert androgens→ estrogen)
- Expanded seminiferous tubules with large Sertoli cells with pale cytoplasm accompanied by prominent basement membrane deposits around and within tubules (→)

OTHER HIGH YIELD POINTS

- Almost **exclusively in Peutz-Jegher's syndrome (think: like SCTATs!)**



FIBROMA/THECOMA

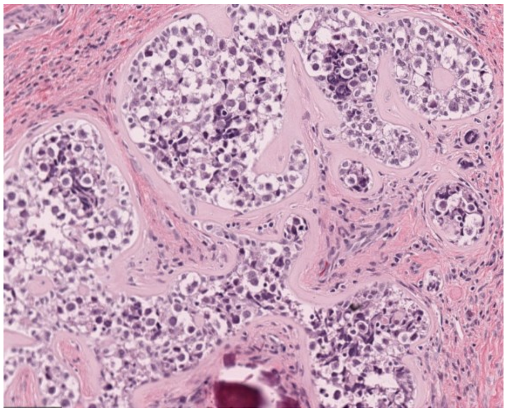
MORPHOLOGY

- Sex cord-stromal tumor of testis resembling ovarian fibroma or thecoma
- **Uniform, spindle to ovoid cells** growing in short, intersecting fascicles or **storiform growth pattern**
- **Reticulin staining shows collagen deposition around individual tumor cells**

OTHER HIGH YIELD POINTS

- Extremely **rare**
- Always **benign**
- Occurs mainly in **adults**
- Often in testis but may rarely be in pretesticular region

GCNIS with eosinophilic basement membrane-like material and calcification



GONADOBLASTOMA

MORPHOLOGY

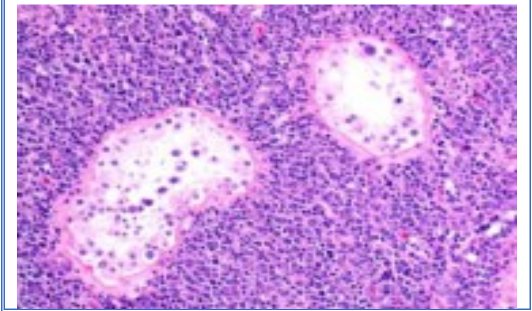
- Tumor composed of a **mixture of germ cells (GCNIS and spermatagonium) and immature sex cord-stromal cells (granulosa cell)**
- Tumor cells arranged in round nested pattern with round deposits of eosinophilic basement membrane-like material
- Frequent **calcifications** can be seen
- **IHC: CD117+ and inhibin negative**

OTHER HIGH YIELD POINTS

- Extremely rare premalignant lesion
- Can be **bilateral (40%)**
- Occurs mainly in dysgenetic gonads
- May progress to **invasive germ cell tumor, often seminoma**

Path Presenter

DLBCL



HEMATOPOIETIC MALIGNANCY

MORPHOLOGY

- Malignant lymphoma is **most common testicular tumor in men over 50 years**
- Can be **primary or part of systemic involvement**
- Secondary involvement is more common than primary lymphoma
- Diffuse Large B-Cell Lymphoma(DLBCL) **comprises ~90% of primary testicular lymphomas**
- Often obliterate the seminiferous tubules centrally with peripheral intertubular spread
- IHC: Same stains as elsewhere

OTHER TUMORS

RETE TESTIS ADENOCARCINOMA

- **Very** rare
- **Malignant gland forming tumor of rete epithelium**
- **Diagnosis** of exclusion (rule out similar primary and mesothelioma)
- **Poor prognosis**

OVARIAN-TYPE EPITHELIAL TUMORS

- Resemble entire spectrum of ovarian type epithelial tumors
- Most **commonly Serous (borderline) and Mucinous tumor**

RETE TESTIS ADENOMA

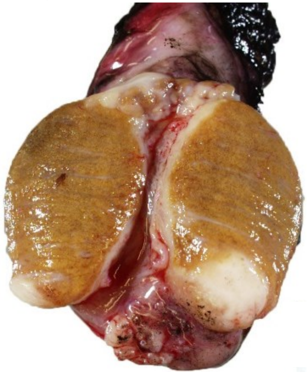
- Very **rare**
- Benign tumor of rete epithelium
- Spectrum from packed tubules (adenoma) to tumors with a cystic component (cystadenoma), papillary architecture (papillary cystadenoma), or glands with prominent fibrous tissue (adenofibroma)

MYOID GONADAL STROMAL TUMOR

- **Spindle cell tumor** with features of gonadal stroma and smooth muscle
- Circumscribed **lesion near rete testis**
- Densely packed **spindled cells arranged in short fascicles**
- **IHC: (+)SF1, FOXL2, SMA, S100**

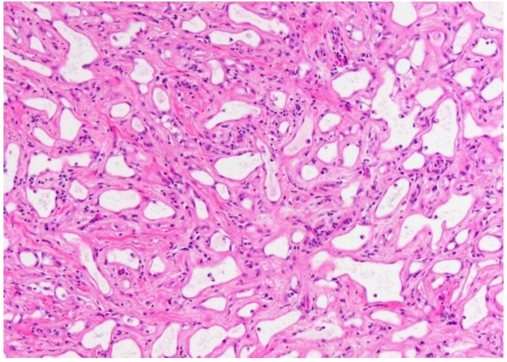
PARATESTICULAR TUMORS

Small, well-circumscribed, white-tan, homogeneous mass



Path Presenter

Gland like microcystic spaces with cuboidal cells

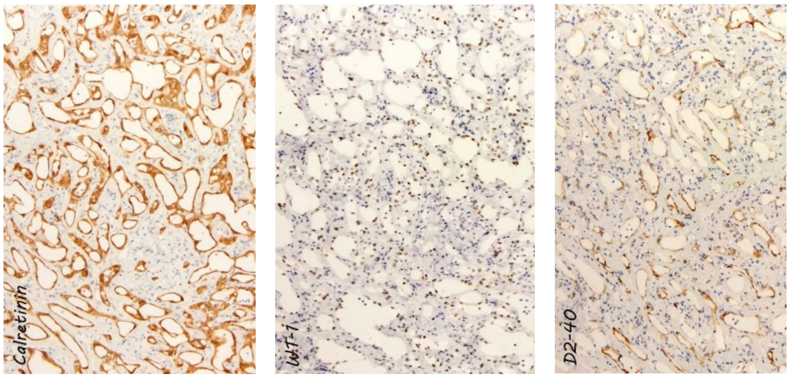


Credit: Phoenix Bell MD @PhoenixBellMD

ADENOMATOID TUMOR

MORPHOLOGY

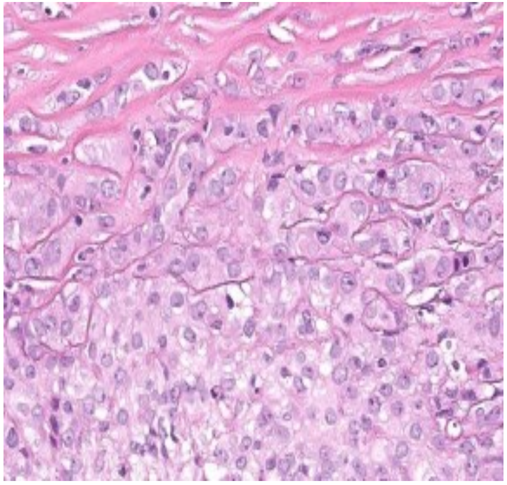
- **Benign** proliferation of mesothelial cells
- Most common neoplasm of Para testicular region
- Small, well-circumscribed, white-tan, homogeneous, firm mass usually < 2cm
- Irregularly shaped gland-like **microcystic spaces composed of flattened or cuboidal cells with associated fibrous stroma and lymphoid aggregates**
- Helpful feature: "thread-like bridging strands, sometimes signet ring-like vacuolated cells
- IHC: Positive for all Mesothelial markers: **D2-40, Calretinin, WT-1, CK5/6 , AE1/AE3**
- Rarely, may have necrosis and extend into testicular parenchyma but these features have no prognostic impact



Calretinin WT-1 D2-40

13. MALE GENITAL PATHOLOGY

Malignant Mesothelioma invading testis



MALIGNANT MESOTHELIOMA

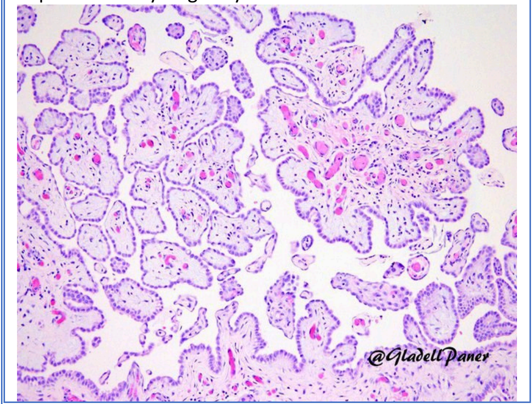
MORPHOLOGY

- Mass envelops testicle, often invading it. (**Invasion is the key feature**)
- Tumor cells show hyperchromatic nucleus with frequent mitosis
- Foam cells and psammoma bodies can be seen
- Majority are epithelial with variable growth pattern (papillary or tubulopapillary)
- Can be biphasic with rare subtypes including, sarcomatoid, desmoplastic, clear cell etc.
- IHC: Positive for all Mesothelial markers: **D2-40, Calretinin, WT-1, CK5/6 , CK AE1/AE3**

OTHER HIGH YIELD POINTS

- Malignant proliferation of mesothelial cells
- 2nd most common malignant tumor in pretesticular region
- Rare, usually **arising from tunica vaginalis**
- Can be associated with hydrocele
- **Not associated with asbestos**

Papillae lined by single layer of cuboidal cells



WELL-DIFFERENTIATED PAPILLARY MESOTHELIAL TUMOR (WDPMT)

MORPHOLOGY

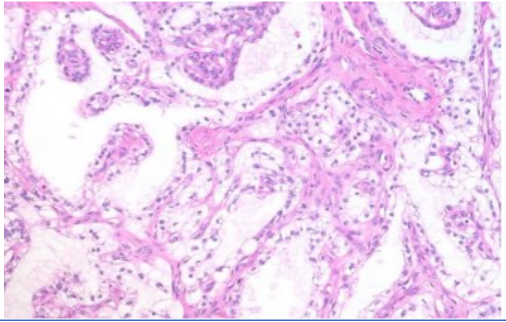
- Tumor shows **papillary architecture with stromal cores**
- Papillae are lined by single layer of bland cuboidal cells
- Rare pseudoinclusions can be seen
- Microinvasion can be seen

OTHER HIGH YIELD POINTS

- WDPMT is distinct entity from malignant mesothelioma
- Rare, **usually arising from tunica vaginalis**
- Most cases are associated with hydrocele

Path Presenter

Papillary Cystadenoma of the Epididymis



PAPILLARY CYSTADENOMA OF THE EPIDIDYMIS

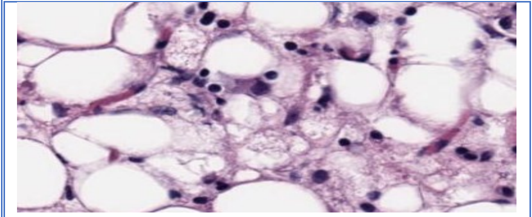
MORPHOLOGY

- Cystic structures that are focally papillary, resembling papillary clear cell carcinoma
- Clear columnar/cuboidal cells with abundant clear cytoplasm
- Frequent **reverse nuclear polarity**
- Colloid-like secretions
- **Immunophenotypically like papillary clear cell RCC**

OTHER HIGH YIELD POINTS

- Rare**, Benign** tumor of Epididymal ducts
- Associated with **von Hippel-Lindau syndrome** (but is more often sporadic)

OTHER MESENCHYMAL TUMORS



Well Differentiated Liposarcoma

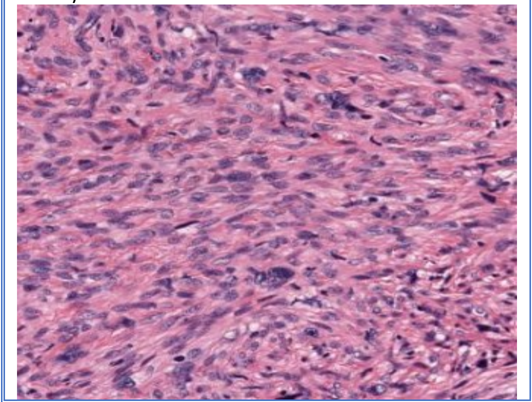
LIPOMA

- **Most common mesenchymal tumor of pretesticular region**
- **Benign tumor** consisting of entirely **mature adipocytes**

WELL-DIFFERENTIATED LIPOSARCOMA

- **Common Para testicular sarcoma**
- **Mature** adipocytes with enlarged, hyperchromatic stromal cell separated by fibrous bands

Leiomyosarcoma



- **Occasional lipoblasts** can be seen.
- Can see inflammation/myxoid change.
- **FISH for MDM2 and CDK4 amplification highly sensitive and specific**

OTHER HIGH YIELD POINTS

- **If large tumor or questionable atypia→ consider getting FISH**
- **Can recur** but won't metastasize unless dedifferentiate or high grade

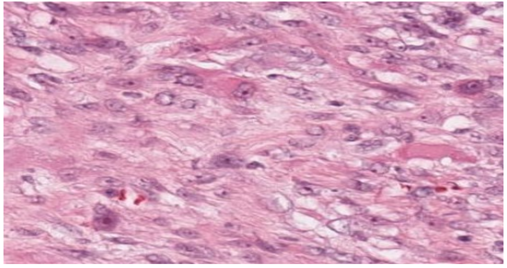
LEIOMYOMA

- Another common lesion in pretesticular region.
- **Benign tumor consisting of entirely bland smooth muscle**
- Spindle cells with **"cigar-like" blunt nuclei** growing in fascicles

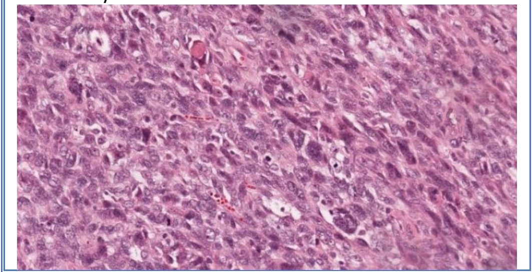
LEIOMYOSARCOMA

- Features of malignancy :Significant atypia, mitoses, and/or tumor necrosis
- **IHC: Positive for Desmin, SMA, H-Caldesmon, Calponin**

Rhabdomyoma



Rhabdomyosarcoma



RHABDOMYOMA

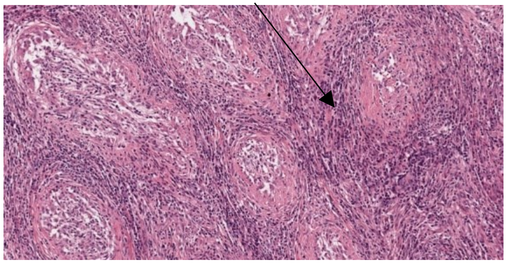
- **Benign tumor of skeleton muscle** differentiation
- Very **rare**, most often **adolescents**
- **Well circumscribed**, **un encapsulated**
- Sheets of large cells, cells are round or polygonal with abundant eosinophilic fibrillar or granular cytoplasm with frequent cross striations and intracytoplasmic rod-like inclusions
- Nuclei are small, round and vesicular, may have prominent nucleoli
- May have **spider cells with vacuolated cytoplasm** (cells resemble spider webs)
- **Variable glycogen and lipid**
- **No mitotic activity, no atypia**

RHABDOMYOSARCOMA

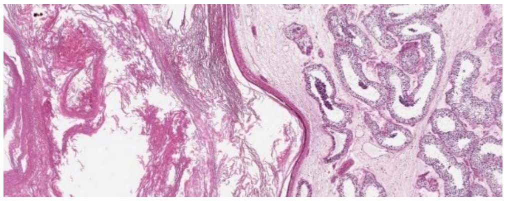
- Often in **children or young adults**
- Embryonal subtype with primitive round or spindled cells and
- Variable **eosinophilic rhabdomyoblasts** with abundant eccentric cytoplasm
- Often **good prognosis**
- **IHC: MyoD1, Myogenin, Desmin**

BENIGN TESTICULAR LESIONS

Inflammatory infiltrates surrounding seminiferous tubules



Cyst wall lined by keratinized squamous epithelium



IDIOPATHIC GRANULOMATOUS ORCHITIS

MORPHOLOGY

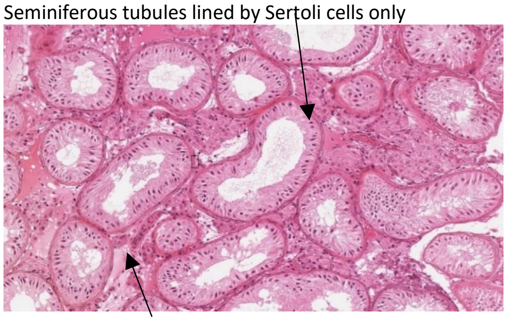
- Rare, benign unilateral enlargement of testes
- Microscopically chronic inflammation surrounding seminiferous tubules and interstitium (lymphocytes and plasma cells)
- Giant cells and histiocytes may be seen
- Differential diagnosis includes lymphoma, infection, and granulomatous inflammation associated with seminoma

EPIDERMOID CYST TESTIS

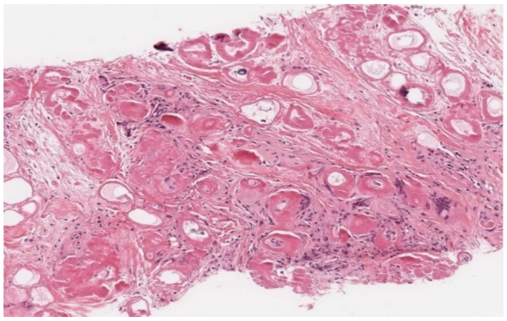
MORPHOLOGY

- Cyst wall lined by keratinized squamous epithelial containing a granular cell layer
- Cyst filled with keratinous material
- Granulomatous reaction following cyst rupture can be seen
- No adnexal structures, no other tissue types are seen
- Grossly intratesticular cyst containing keratinous material

Seminiferous tubules lined by Sertoli cells only



Thicker basement membranes



Nodular deposits of amorphous eosinophilic material

OTHER HIGH YIELD POINTS

- Rare benign cyst of the testis
- Usually seen in young adults

SERTOLI ONLY SYNDROME

MORPHOLOGY

- Seminiferous tubules lined by Sertoli cells only without presence of germ cells
- Focal areas of normal/preserved spermatogenesis may be seen
- Seminiferous tubules show thicker basement membranes with narrower lumens

OTHER HIGH YIELD POINTS

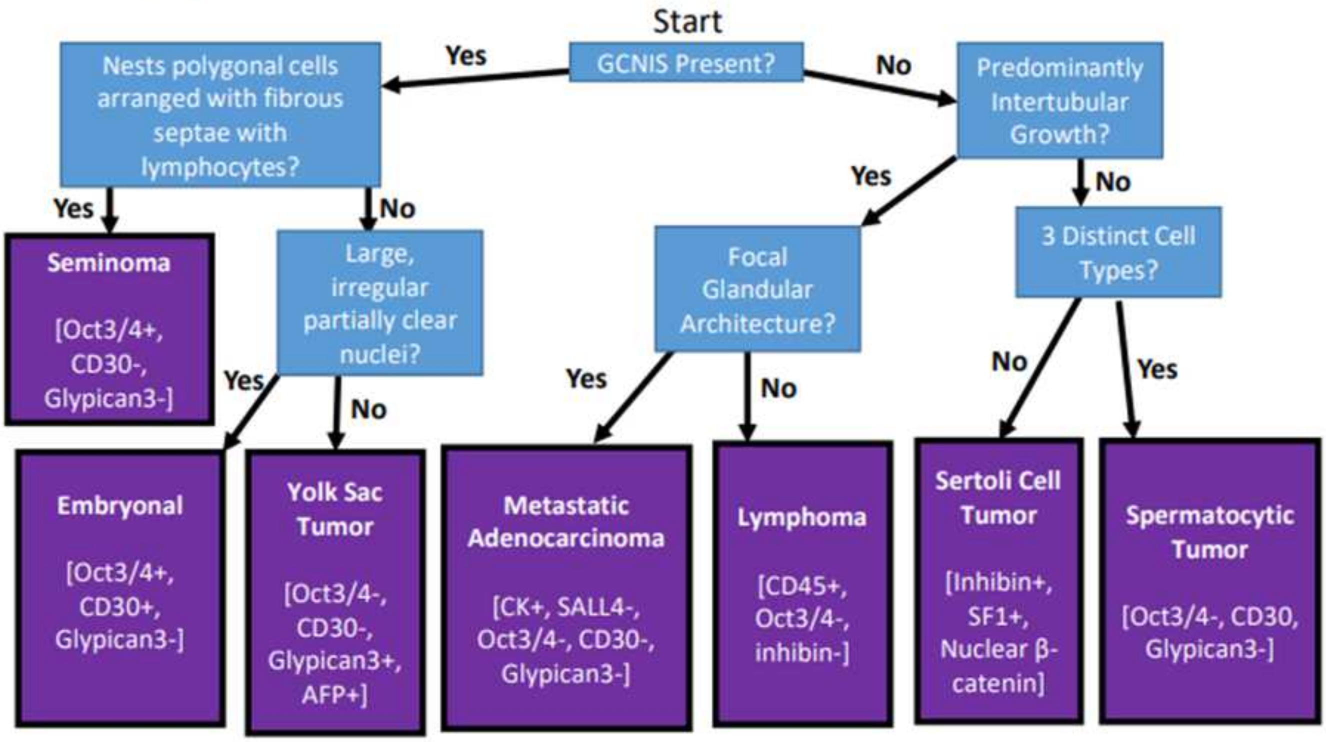
- Also known as del Castillo syndrome or germ cell aplasia
- Can be primary or secondary
- Most common causes of azoospermia in infertile men
- Low or absent spermatogenesis
- Diagnosis is usually made based on testicular biopsy finding

AMYLOIDOSIS- PROSTATE

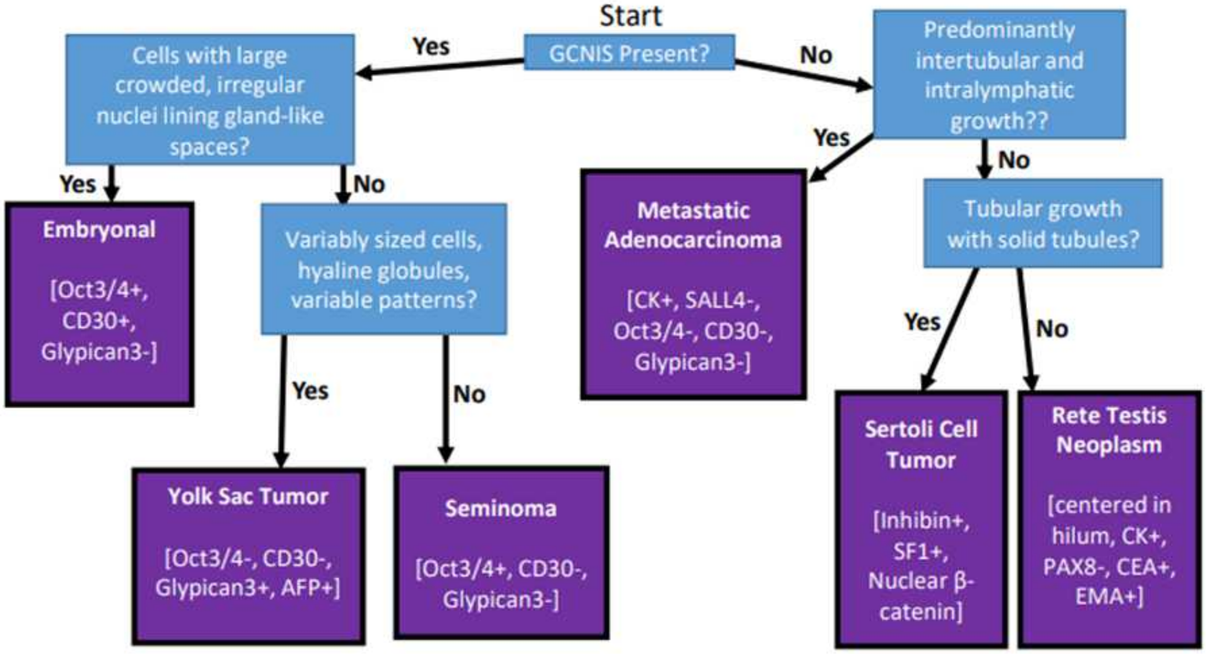
- Linear or nodular deposits of amorphous eosinophilic fibrillar material
- Highlighted with Congo Red with “Apple-green” birefringence

Algorithms modified from: Urologic Surgical Pathology. Liang Chen et al. 2020.

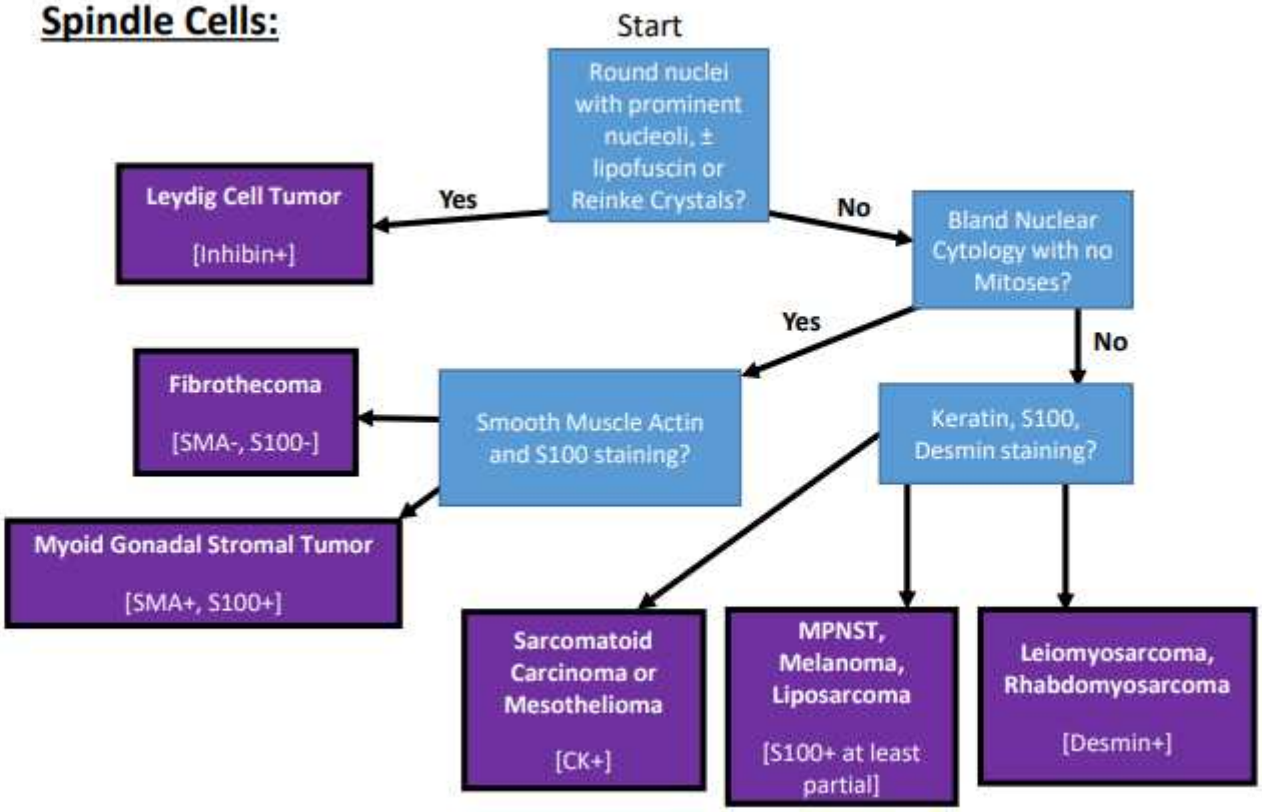
Clear Cytoplasm:


Start
GCNIS Present?
Yes
No
Nests polygonal cells arranged with fibrous septae with lymphocytes?
Yes
No
Seminoma
[Oct3/4+, CD30-, Glypican3-]
Large, irregular partially clear nuclei?
Yes
No
Embryonal
[Oct3/4+, CD30+, Glypican3-]
Yolk Sac Tumor
[Oct3/4-, CD30-, Glypican3+, AFP+]
Predominantly Intertubular Growth?
Yes
No
Focal Glandular Architecture?
Yes
No
Metastatic Adenocarcinoma
[CK+, SALL4-, Oct3/4-, CD30-, Glypican3-]
Lymphoma
[CD45+, Oct3/4-, inhibin-]
3 Distinct Cell Types?
No
Yes
Sertoli Cell Tumor
[Inhibin+, SF1+, Nuclear β-catenin]
Spermatocytic Tumor
[Oct3/4-, CD30, Glypican3-]

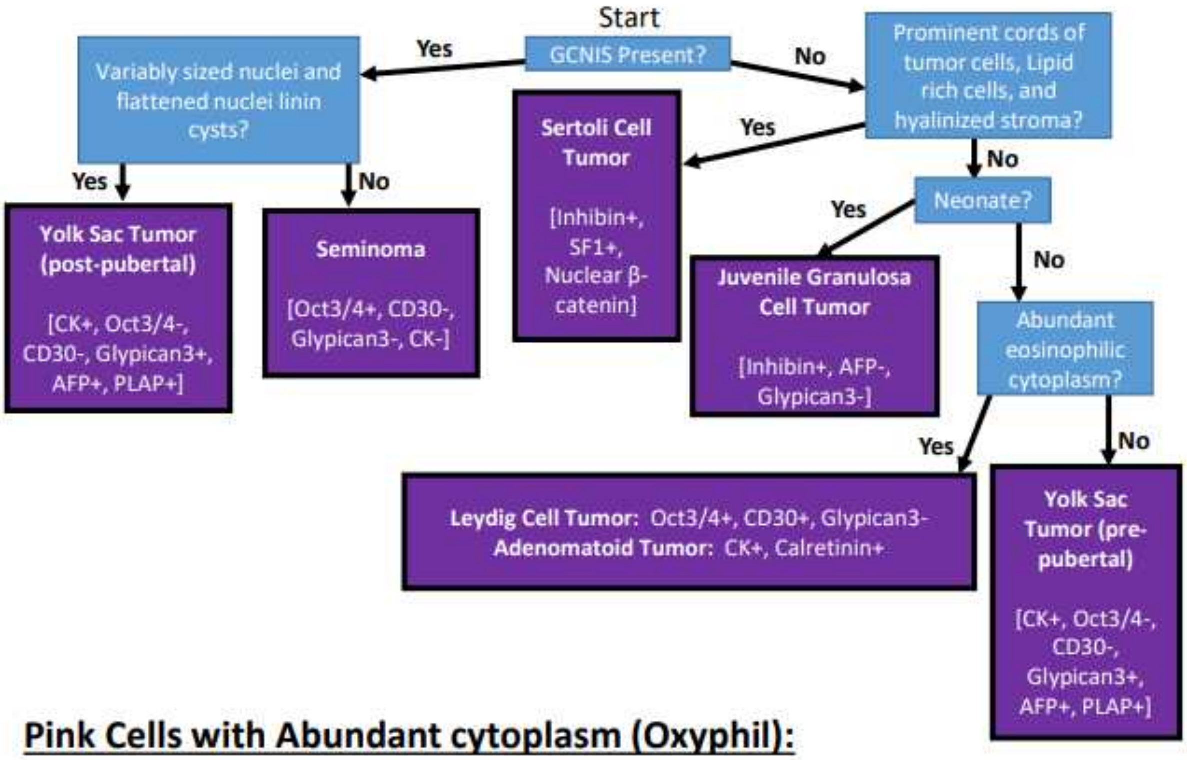
Glandular and/or Tubular growth:


Start
GCNIS Present?
Yes
Cells with large crowded, irregular nuclei lining gland-like spaces?
Yes
Embryonal
[Oct3/4+, CD30+, Glypican3-]
No
Variably sized cells, hyaline globules, variable patterns?
Yes
Yolk Sac Tumor
[Oct3/4-, CD30-, Glypican3+, AFP+]
No
Seminoma
[Oct3/4+, CD30-, Glypican3-]
No
Predominantly intertubular and intralymphatic growth??
Yes
Metastatic Adenocarcinoma
[CK+, SALL4-, Oct3/4-, CD30-, Glypican3-]
No
Tubular growth with solid tubules?
Yes
Sertoli Cell Tumor
[Inhibin+, SF1+, Nuclear β-catenin]
No
Rete Testis Neoplasm
[centered in hilum, CK+, PAX8-, CEA+, EMA+]

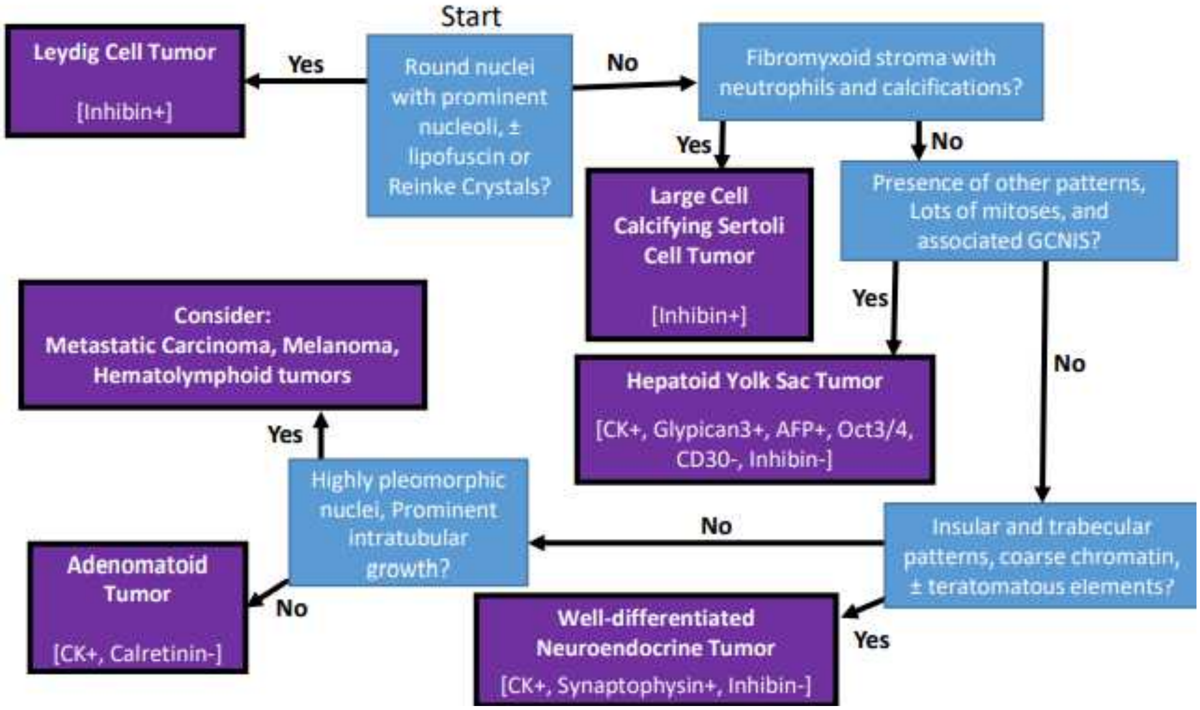
Spindle Cells:

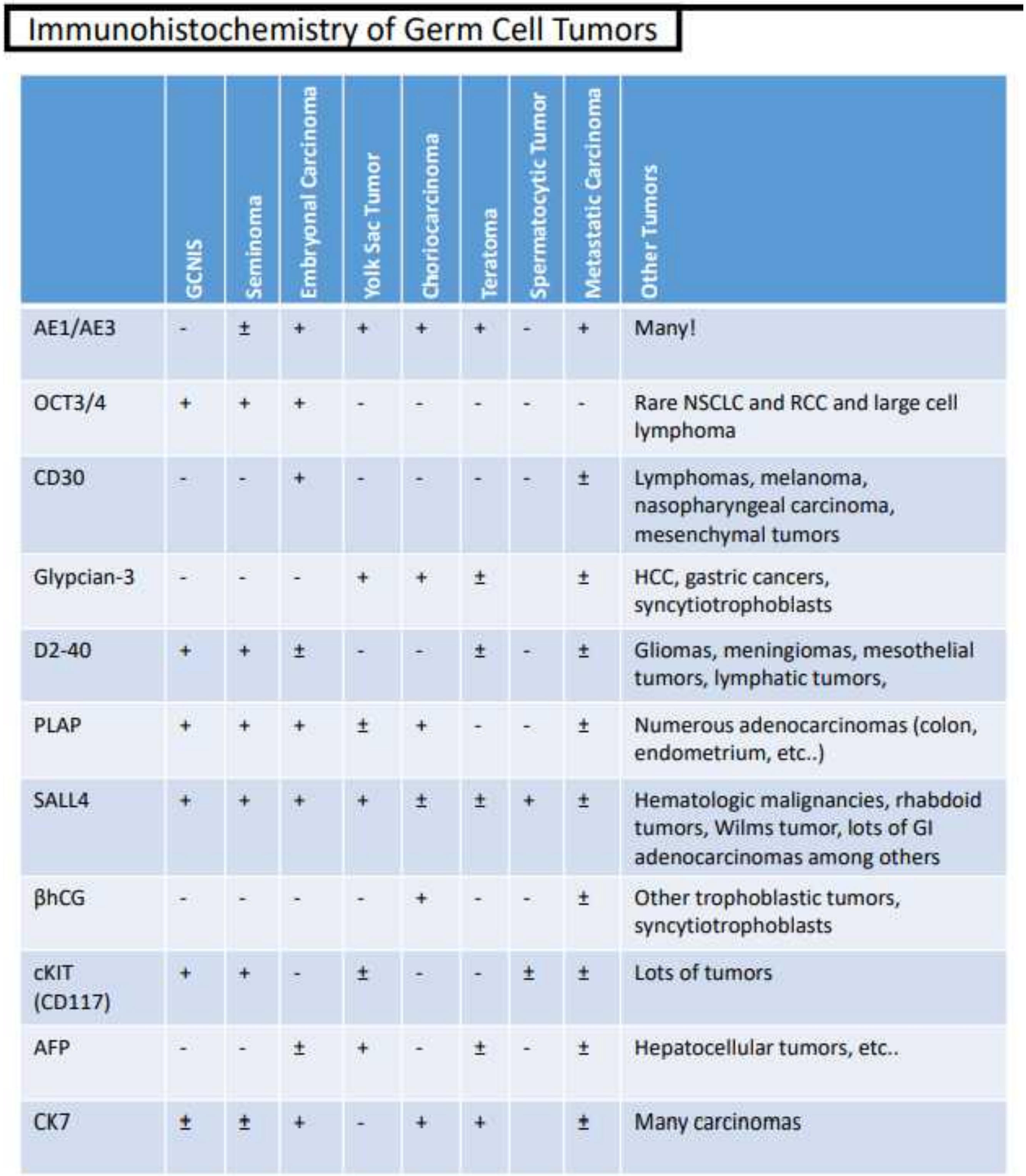

Start
Round nuclei with prominent nucleoli, ± lipofuscin or Reinke Crystals?
Yes
Leydig Cell Tumor
[Inhibin+]
No
Bland Nuclear Cytology with no Mitoses?
Yes
Smooth Muscle Actin and S100 staining?
Fibrothecoma
[SMA-, S100-]
Myoid Gonadal Stromal Tumor
[SMA+, S100+]
No
Keratin, S100, Desmin staining?
Sarcomatoid Carcinoma or Mesothelioma
[CK+]
MPNST, Melanoma, Liposarcoma
[S100+ at least partial]
Leiomyosarcoma, Rhabdomyosarcoma
[Desmin+]

Microcystic:


Start
GCNIS Present?
Yes
Variably sized nuclei and flattened nuclei linin cysts?
Yes
Yolk Sac Tumor (post-pubertal)
[CK+, Oct3/4-, CD30-, Glypican3+, AFP+, PLAP+]
No
Seminoma
[Oct3/4+, CD30-, Glypican3-, CK-]
No
Prominent cords of tumor cells, Lipid rich cells, and hyalinized stroma?
Yes
Sertoli Cell Tumor
[Inhibin+, SF1+, Nuclear β-catenin]
No
Neonate?
Yes
Juvenile Granulosa Cell Tumor
[Inhibin+, AFP-, Glypican3-]
No
Abundant eosinophilic cytoplasm?
Yes
Leydig Cell Tumor: Oct3/4+, CD30+, Glypican3-
Adenomatoid Tumor: CK+, Calretinin+
No
Yolk Sac Tumor (pre-pubertal)
[CK+, Oct3/4-, CD30-, Glypican3+, AFP+, PLAP+]

Pink Cells with Abundant cytoplasm (Oxyphil):


Start
Round nuclei with prominent nucleoli, ± lipofuscin or Reinke Crystals?
Yes
Leydig Cell Tumor
[Inhibin+]
No
Fibromyxoid stroma with neutrophils and calcifications?
Yes
Large Cell Calcifying Sertoli Cell Tumor
[Inhibin+]
No
Presence of other patterns, Lots of mitoses, and associated GCNIS?
Yes
Hepatoid Yolk Sac Tumor
[CK+, Glypican3+, AFP+, Oct3/4, CD30-, Inhibin-]
No
Insular and trabecular patterns, coarse chromatin, ± teratomatous elements?
Yes
Well-differentiated Neuroendocrine Tumor
[CK+, Synaptophysin+, Inhibin-]
No
Highly pleomorphic nuclei, Prominent intratubular growth?
Yes
Consider:
Metastatic Carcinoma, Melanoma, Hematolymphoid tumors
No
Adenomatoid Tumor
[CK+, Calretinin-]

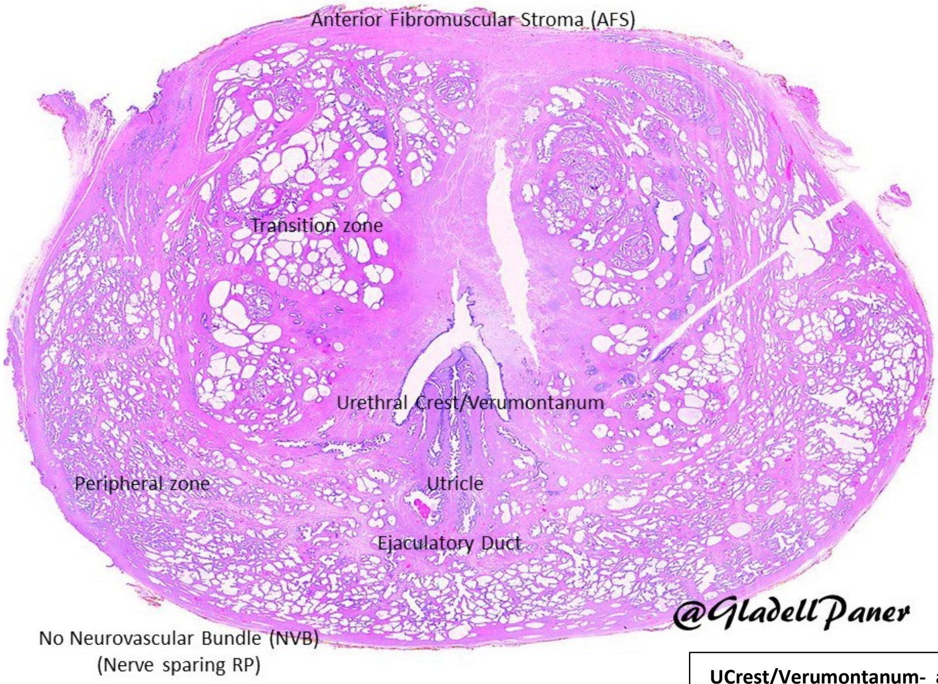


Immunohistochemistry of Germ Cell Tumors

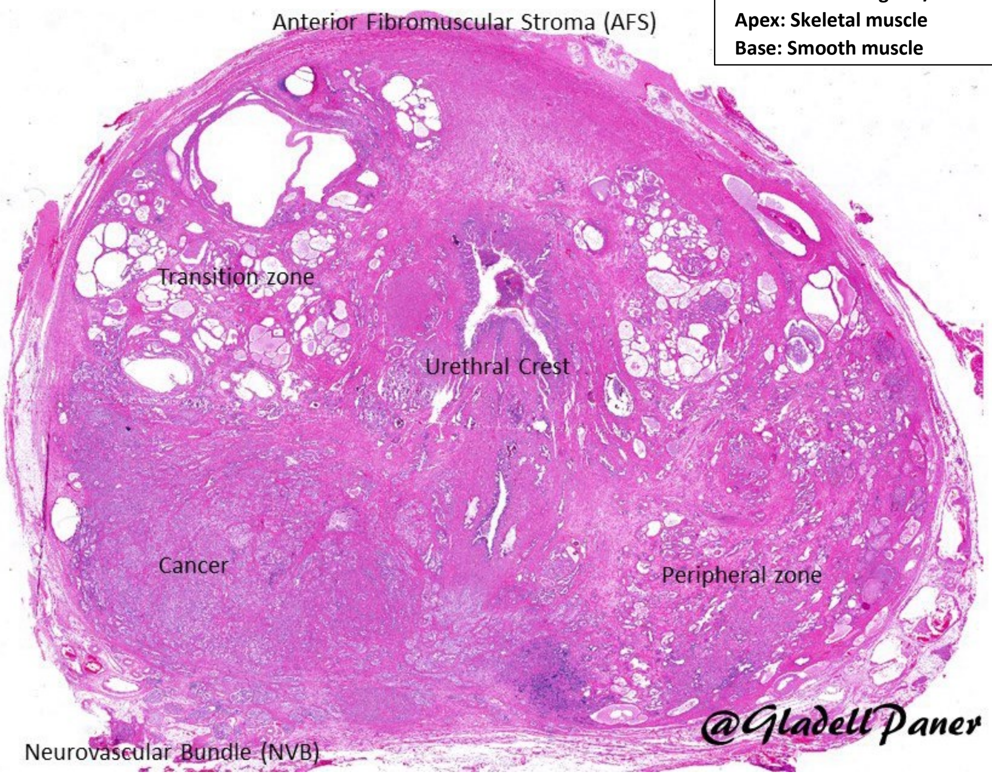
	GCNIS	Seminoma	Embryonal Carcinoma	Yolk Sac Tumor	Choriocarcinoma	Teratoma	Spermatocytic Tumor	Metastatic Carcinoma	Other Tumors
AE1/AE3	-	±	+	+	+	+	-	+	Many!
OCT3/4	+	+	+	-	-	-	-	-	Rare NSCLC and RCC and large cell lymphoma
CD30	-	-	+	-	-	-	-	±	Lymphomas, melanoma, nasopharyngeal carcinoma, mesenchymal tumors
Glypcian-3	-	-	-	+	+	±		±	HCC, gastric cancers, syncytiotrophoblasts
D2-40	+	+	±	-	-	±	-	±	Gliomas, meningiomas, mesothelial tumors, lymphatic tumors,
PLAP	+	+	+	±	+	-	-	±	Numerous adenocarcinomas (colon, endometrium, etc..)
SALL4	+	+	+	+	±	±	+	±	Hematologic malignancies, rhabdoid tumors, Wilms tumor, lots of GI adenocarcinomas among others
βhCG	-	-	-	-	+	-	-	±	Other trophoblastic tumors, syncytiotrophoblasts
cKIT (CD117)	+	+	-	±	-	-	±	±	Lots of tumors
AFP	-	-	±	+	-	±	-	±	Hepatocellular tumors, etc..
CK7	±	±	+	-	+	+		±	Many carcinomas

Modified from: WHO classification of Tumors of the Urinary System and Male Genital Organs. 4th ed.

PROSTATE


Anterior Fibromuscular Stroma (AFS)
Transition zone
Urethral Crest/Verumontanum
Peripheral zone
Utricle
Ejaculatory Duct
@GladellPaner
No Neurovascular Bundle (NVB)
(Nerve sparing RP)

UCrest/Verumontanum- anterior
AFS- anterior Regular/flatter- Posterior
Apex: Skeletal muscle
Base: Smooth muscle

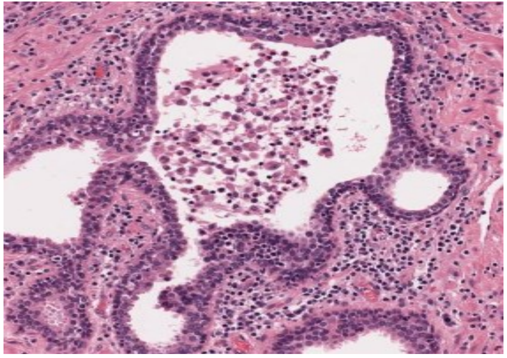

Anterior Fibromuscular Stroma (AFS)
Transition zone
Urethral Crest
Cancer
Peripheral zone
@GladellPaner
Neurovascular Bundle (NVB)

13. MALE GENITAL PATHOLOGY

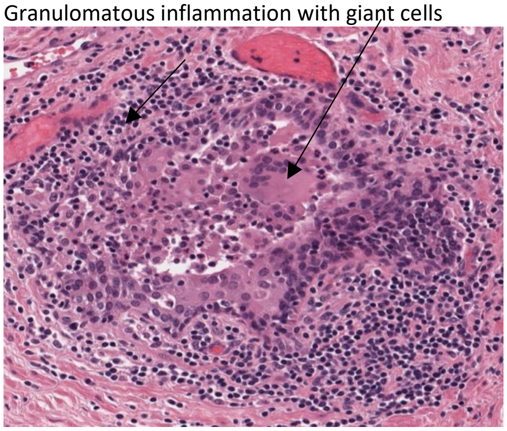
PROSTATE

PROSTATITIS

Chronic inflammatory infiltrates in lumen



Granulomatous inflammation with giant cells



PROSTATITIS

MORPHOLOGY

- Clinically classified as **bacterial prostatitis** (acute and chronic) and **abacterial prostatitis (chronic)**
- Chronic a bacterial prostatitis is most common
- Clinically tender, swollen prostate glands and/or urinary tract infection
- **E coli, gram-negative rods and enterococcus are most common infectious cause of prostatitis**
- **Granulomatous prostatitis** can be seen in patients **after BCG therapy for bladder cancer**

ACUTE PROSTATITIS

- Characterized by presence of **neutrophils in the glandular lumen** and reactive glandular atypia with prominent nucleoli

CHRONIC PROSTATITIS

- Characterized by presence of **lymphocytes and plasma cells in the glandular lumen and stroma surrounding the glands**

GRANULOMATOUS PROSTATITIS

- Characterized by presence of **granulomatous inflammation with giant cells and plasma cells**
- Seen in patients **post BCG treatment for bladder cancer**
- If infection is cause is the suspected special stains such as GMS, AFB and PAS is recommended

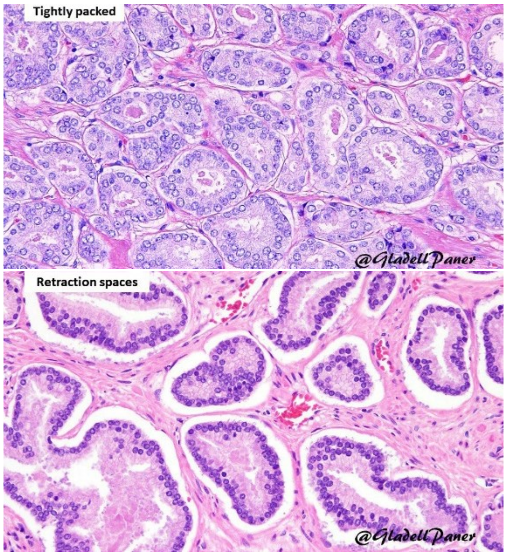
OTHER HIGH YIELD POINTS

- **Acute prostatitis can sometimes be the cause of clinically elevated PSA**

Path Presenter

TUMORS OF PROSTATE

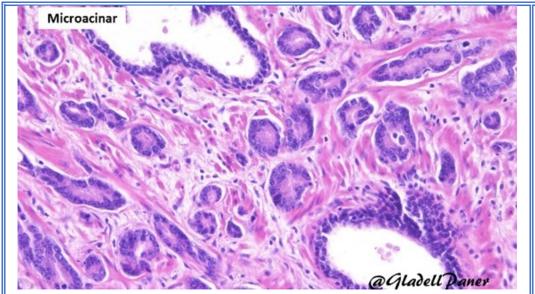
Patern 3

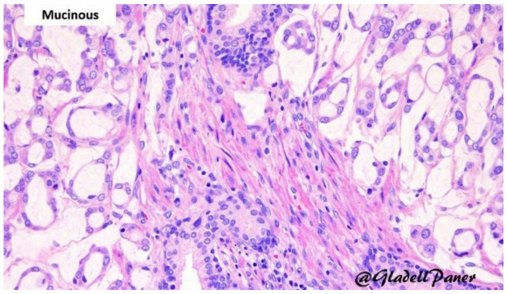


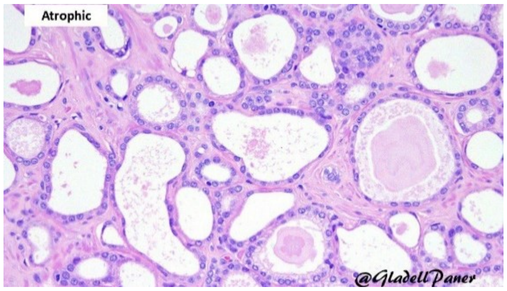
ACINAR ADENOCARCINOMA

MORPHOLOGY

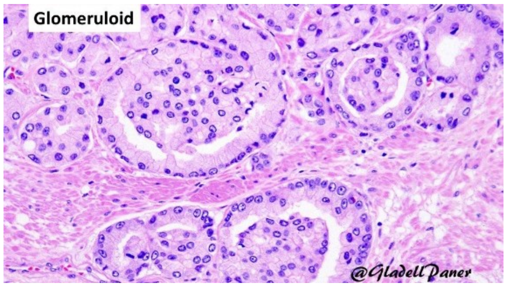
- **Most common type of prostate cancer**
- Most common and second leading cause of cancer death in men
- Prevalence is strongly correlated with age (older = higher prevalence)
- Mostly **multifocal** and **commonly located in posterior/posterolateral peripheral gland**
- Often asymptomatic (early). Locally advanced prostate cancer mimics BPH with urinary symptoms.
- **Bone is common site of metastasis** (bone pain & pathologic fractures)
- Crowded small glands with sharp luminal borders
- **Haphazard, infiltrative pattern of growth**
- Tumor cells shows nuclear enlargement, prominent nucleoli, and amphophilic cytoplasm, **absent basal cell layer**
- Mitotic figures and apoptotic bodies can be seen
- Luminal contents: Blue-tinged mucin, Pink amorphous secretions, crystalloids can be present
- Usually lack desmoplastic stroma. When present, often associated with high-grade carcinoma

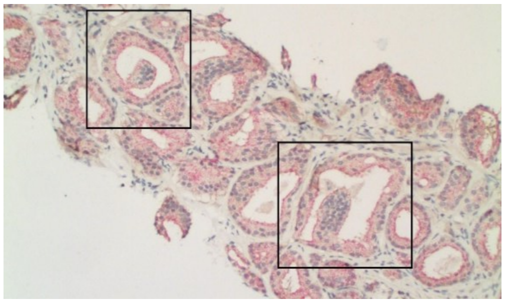






Pattern 4 Glomerization





Pattern 4: Glomerization: highlighted by IHC Credit: Ankur Sangoi@slusagar

IMMUNOHISTOCHEMICAL STAINS

- Prostate Specific Antigen (PSA), Prostatic Acid Phosphatase (PSAP), Protein-sensitive markers (~95%)
- **NKX3.1, most specific marker**
- Other markers are of limited utility (ERG, AR, AMACR) due to poor sensitivity or specificity
- **PIN4 cocktail (AMCAR, and Basal cell marker HMWCK and p63)** is commonly used
- **Immunohistochemistry is primarily useful to disprove cancer, not to prove cancer**
- **PSA & PSAP expression can decrease after androgen deprivation therapy**

OTHER HIGH YIELD POINTS

- Fibroblasts may mimic basal cells (use IHC to high highlight)

Benign Glands	Prostatic Adenocarcinoma
Big, regularly spaced glands	Small, infiltrative glands with haphazard and variable spacing
Papillary infoldings	Sharp luminal contours
Small nuclei without nucleoli	Large nuclei with prominent nucleoli and frequent hyperchromasia
Abundant pale, clear apical cytoplasm	Amphophilic cytoplasm
Corpora amylacea	Eosinophilic or blue mucin secretions

Path presenter

PP link PP link

GLEASON SCORE

- Recommended for all prostate specimen containing adenocarcinoma
- **Gleason score is sum of primary (most predominant) and secondary (second most predominant) pattern of tumor glands**
- When no secondary pattern exists, the primary pattern is double (e.g., 3+3=6, 4+4=8, 5+5=10)
- The percentage of pattern 4 should be recorded in all Gleason score 7 (3+4, 4+3)
- For tumors with Gleason score greater than 7 currently there is no consensus on reporting the percentage of pattern 4 or 5 although the percentage has prognostic significance

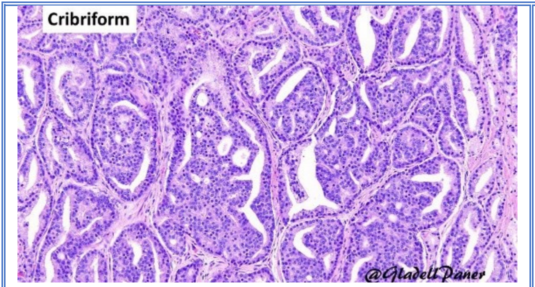
OTHER HIGH YIELD POINTS

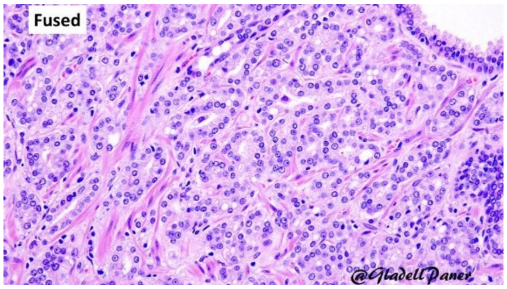
- **Tumors showing treatment effect** (androgen deprivation therapy and radiation therapy) **are not graded**
- **The percentage of pattern 4 should be recorded** in all Gleason score 7 this has a practical importance since patients with Gleason score 7 (3+4 with small amount of **pattern 4 less than or equal to 10% may be eligible for active surveillance)**

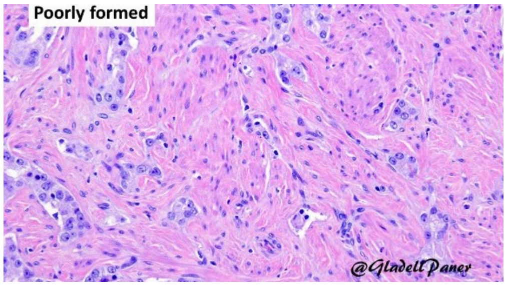
REPORTING OF PROSTATE CANCER

BIOPSY:

1. Most common + Second most common pattern = Score, no tertiary pattern assigned
   - ➢ (e.g., 80% pattern 3 and 20% pattern 4 → 3+4=7)
   - ➢ (e.g., 80% pattern 4 and 20% pattern 3 → 4+3=7)

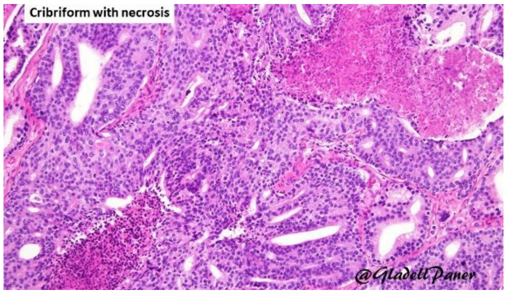


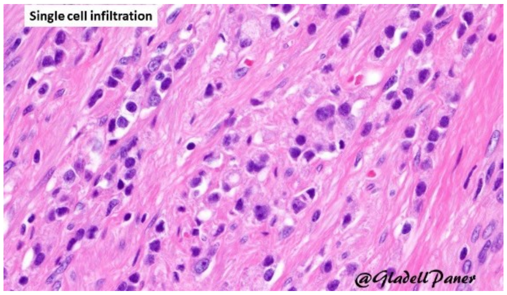




Credit: Gladell PanerMD @GladellPaner

Pattern 5





2. Most common + Highest grade pattern (any amount) = Score, No tertiary pattern assigned
    - ➢ (e.g., Needle biopsies with 87% pattern 3, 10% pattern 4, and 3% pattern 5 →3 + 5 = 8)

PROSTATECTOMIES:

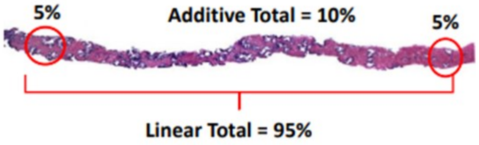
3. Most common + Second most common = Score**,** with tertiary pattern if present

OTHER HIGH YIELD POINTS

- No tertiary pattern assigned in biopsy pattern
- **In the setting of high-grade cancer ignore lower-grade patterns if they occupy less than 5% of the area of the tumor**
    - ➢ (e.g., 98% pattern 4 and 2% pattern 3 → 4+4=8)
- **High-grade tumor of any quantity should be included**
    - ➢ (e.g., 98% pattern 3 and 2% pattern 4 → 3+4=7)
- **Discontinuous focus: controversial, no consensus but several studies have shown the total linear method correlates better with prostatectomy findings**

Biopsy Report must include

- ➢ Specimen/location, Gleason Score and Grade Group
- ➢ Percentage of pattern 4 in cases with a Gleason score 7
- ➢ Number of cores with cancer (or for TURPs the number of positive chips and total number of chips)
- ➢ Perineural invasion or extra prostatic extension (if present)
- ➢ Linear extent of cancer in each core (percentage and/or length)

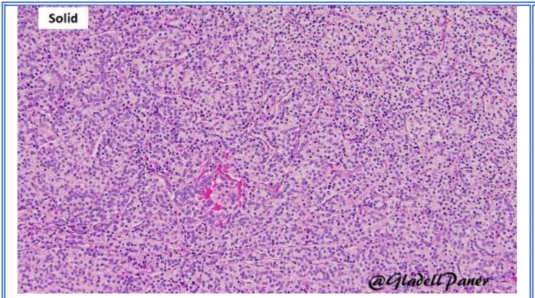


e.g., PROSTATE, LEFT MEDIAL, BIOPSY:
- Prostatic adenocarcinoma, Gleason score 3+4=7 (Grade group 2)
- Involving one of one core (1/1)
-.Grade 4 represents approximately 10% of the carcinoma volume
- Two focus 1.1mm/11mm of core/ 10% of core
- Perineural invasion is identified

e.g., PROSTATE, LEFT MEDIAL, BIOPSY:
- Prostatic adenocarcinoma, Gleason score 3+4=7 (Grade group 2)
- Involving one of one core (1/1)
-.Grade 4 represents approximately 10% of the carcinoma volume
- Linear focus 9mm/11mm of core/ 95% of core
- Perineural invasion is identified

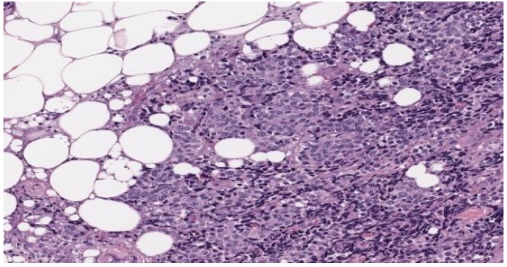
GENETICS

- One of the most heritable cancer types
- This risk is mostly associated with many SNPs with each having relatively low risk/penetrance (but the effect can be multiplicative).
- **TMPRSS2-ERG fusion has been identified as an early molecular event for development of prostate cancer**
- **BRACA2→ significantly increased risk of prostate cancer**
- **Other frequent mutations: TP53, PTEN**

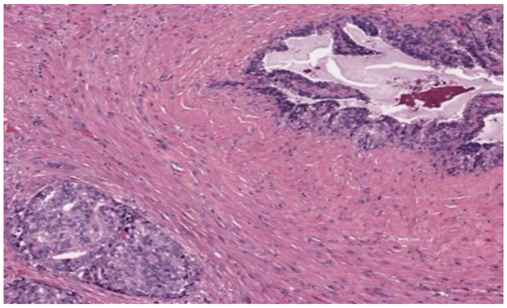


Credit: Gladell PanerMD @GladellPaner

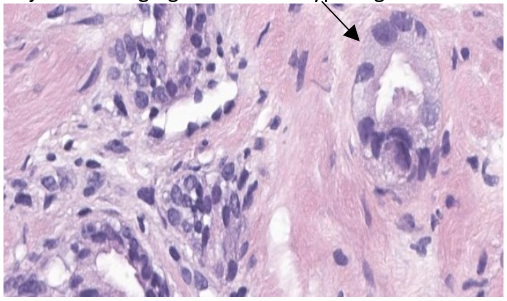
Tumor growing in between fat



Seminal vesicle involvement



Adjacent benign glands Atypical gland



ISUP GRADE GROUPING

- The grade grouping strongly correlated with survival and biochemical recurrence

Grade Group	Gleason Score	Description
1	</= 6	Only individual discrete well-formed glands
2	3+4=7	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands
3	4+3=7	Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands
4	8	-Only poorly formed/fused/cribriform glands -Predominantly well-formed gland and lesser component lacking glands -Predominantly lacking glands and lesser component of well-formed glands
5	9-10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.

EXTRAPROSTATIC EXTENSION

- Presence of **tumor beyond the confines of the prostate gland** (especially in apex and base)
- **Invading fat** (directly touching adipocytes)
- **Involving loose connective tissue** beyond the plane of the prostate (does not need to be directly touching adipocytes)
- **Involving perineural spaces** in the neurovascular bundles
- **Invasion of the urinary bladder neck** (involving the thick intersecting smooth muscle bundles characteristic of the bladder neck region)
- **Seminal vesicle involvement**: invasion of the muscular wall of seminal vesicle (must be Extra prostatic)
- **Identification is very important for staging**!!

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ATYPICAL SMALL ACINAR PROLIFERATION (ASAP)

- **A descriptive term (not an entity) designed to be used when you have a collection of small glands suspicious for cancer but lack definitive diagnostic features or are too small to be certain**
- Managed with clinical **follow-up and repeat biopsy**

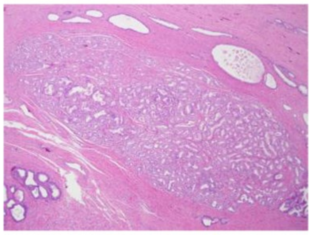
OTHER HIGH YIELD POINTS

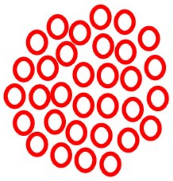
- How many glands do you need to diagnose cancer?
  - There is no absolute number, **at least 3 glands with cytologic/architectural features of cancer**

Path Presenter

GLEASON'S GRADING

1

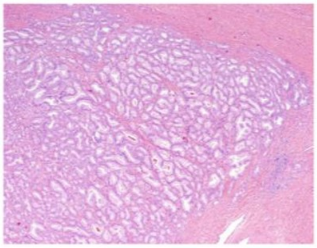


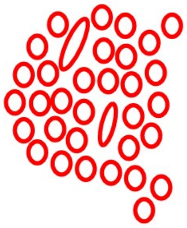


Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini

Should **not** be diagnosed regardless of the type of specimen, with extremely rare exceptions

2



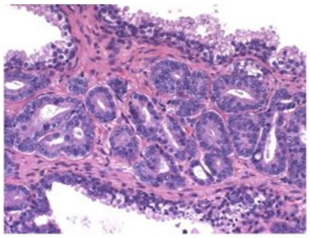


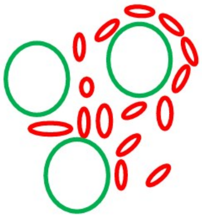
Fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration

Do not diagnose on biopsy, rarely diagnosed regardless of specimen.

Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

3

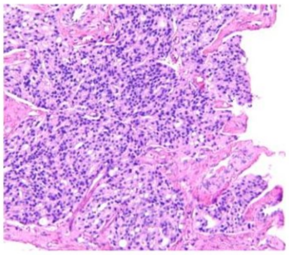


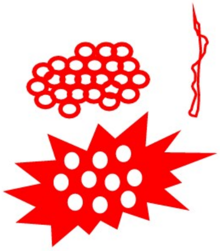


Well-formed glands ***(with lumina)***
Separate, discrete, Non-fused

Infiltration

4



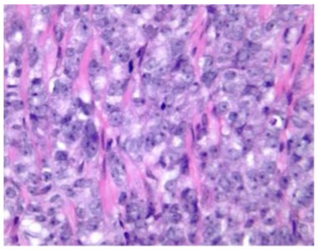


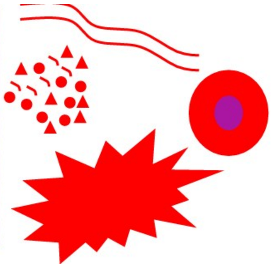
Ill-defined, poorly formed glands
Gland fusion
ALL cribriform glands
Hypernephromatoid
Glomerulations

Ductal Adenocarcinoma (without necrosis)

Often Disqualifies from Active Surveillance

5



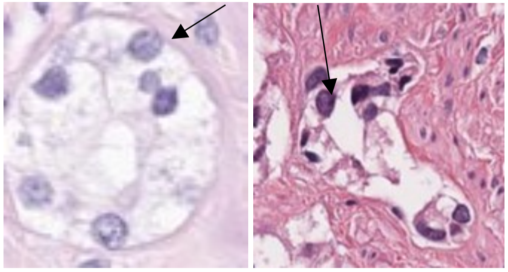


Essentially **no glandular differentiation:**

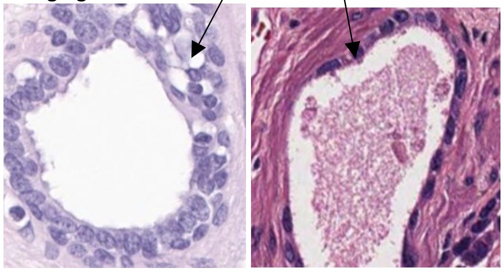
- Solid sheets
- Cords
- Single cells
- Linear arrays

Comedocarcinoma with central necrosis

Tumor glands with ADT and radiation effect



Benign glands with ADT and Radiation effect



NCCN INCLUSION CRITERIA:

Absolute (Low risk):

- Gleason Score ≤6
- PSA <10 ng/mL
- Clinical stage <T2a (Tumor involves one-half of one lobe or less)

(Very low risk):

- Fewer than 3 cores positive, all ≤50%

NCCN PROGRESSION CRITERIA: (initiates transition to curative therapy)

- Gleason grade 4 or 5 on repeat biopsy
- Greater number of positive cores or greater extent of biopsies

TREATMENT EFFECT

- Treatment can be **systemic** (hormone therapy, immunotherapy, chemotherapy) or **local** (radiation) or both
- Androgen deprivation therapy (ADT) or radiation therapy can **show minimal or extensive changes in both benign and malignant glands**

RADIATION THERAPY:

- Benign glands:
  - Show marked radiation atypia, atrophic changes, and basal cell immunophenotype in IHC
- Adenocarcinoma:
  - Often show glands with vacuolated cytoplasm and small inconspicuous nuclei/nucleoli

HORMONAL THERAPY:

- Benign glands:
  - Show diffuse atrophy with prominent basal cells
- Adenocarcinoma:
  - Show atrophic glands with vacuolated cytoplasm and small inconspicuous nuclei/nucleoli

OTHER HIGH YIELD POINTS

- Use stains liberally.
- Do not grade if treatment effect is present (behave better than grade would suggest

ACTIVE SURVEILLANCE

For low and very low risk patients Instead of receiving immediate definitive treatment with curative intent

- **Regular follow-up with serum PSA, digital rectal exam, repeat prostate biopsies (6-12 months after initial), yearly for up to 10 years** (looking for progression)

OTHER HIGH YIELD POINTS

- PNI is allowed
  Excluded if: any variant other than acinar adenocarcinoma (e.g., ductal, sarcomatoid, small cell), intraductal carcinoma

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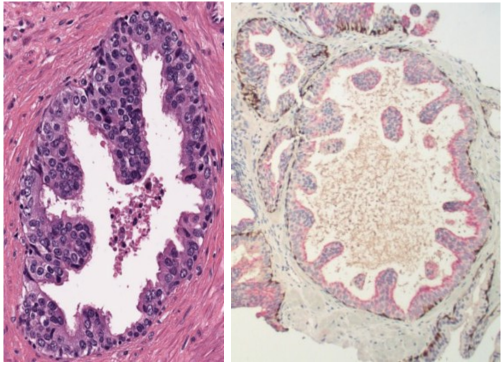
PP link PP link

INTRADUCTAL TUMORS

High grade PIN



PIN-4 staning: High grade PIN, intact p63 in basal cells Credit: Andres Martin Acosta MD @Andres_M_Acosta

HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA ("HGPIN")

MORPHOLOGY

- **Pre-malignant condition**
- Often **multifocal**
- Characterized by cytologic changes (nuclear enlargement, prominent nucleoli hyperchromasia, nuclear overlap, amphophilic cytoplasm) resembling cancer but basal cells are present
- Architecturally these **glands can show tufting, micropapillary and flat growth pattern**

OTHER HIGH YIELD POINTS

- Associated with subsequent detection of cancer (**more HGHPIN→ higher risk**)
- Basal cells may be attenuated

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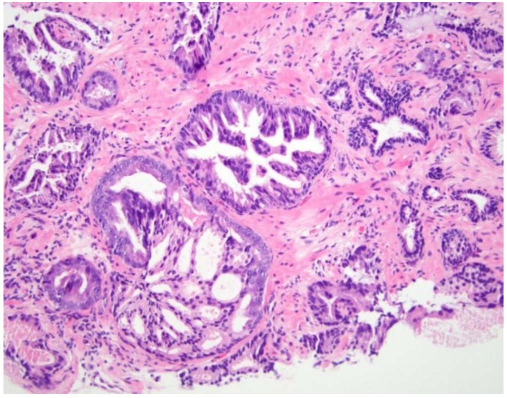
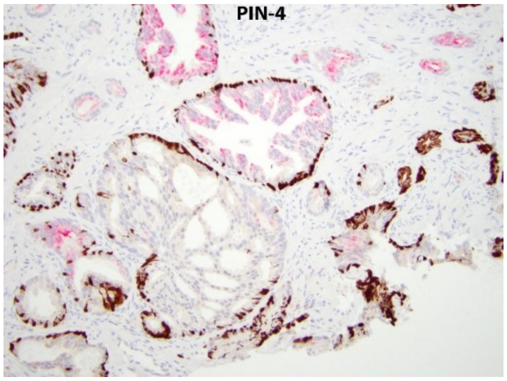
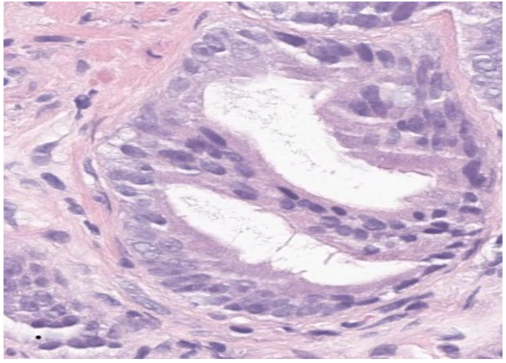
IDC, dense cribriformed gland with comedo necrosis





PIN-4 staining in intraductal carcinoma
Credit: Andres Martin Acosta MD @Andres_M_Acosta



Atypical intraductal proliferation

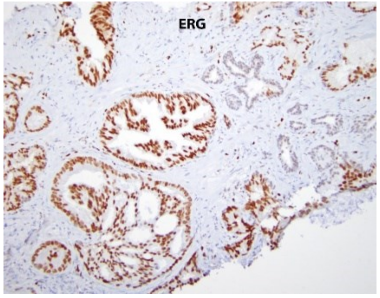
INTRADUCTAL CARCINOMA (IDC)

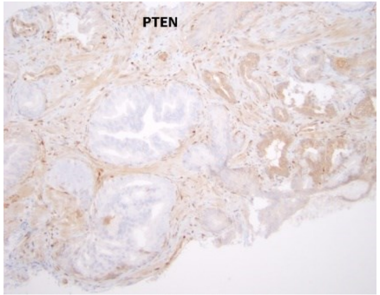
MORPHOLOGY

- **Distinct precursor lesion** (separate from HGPIN)
- **High risk of progression to cancer**
- Malignant proliferation of epithelial cells filling large acini and ducts, with preservation of basal cells
- Architecturally these **glands show with either solid, dense, or loose cribriform and micropapillary pattern**
- Dense cribriform glands: (**Defined as > 50% of gland composed of epithelium relative to luminal spaces**)
- Tumor glands are characterized by **marked nuclear atypia**
- Can show comedonecrosis, and usually are part of intraductal spread of invasive cancer
- IHC often required for diagnosis to demonstrate basal cells
- IDC are not graded

OTHER HIGH YIELD POINTS

- **TMPRSS::ERG fusion and PTEN loss more common in IDC** than HGPIN, (PTEN retained in HGPIN)
- **IDC is strongly associated high Gleason grade**, **high tumor volume** in prostatectomy specimen and metastasis)





PROPOSED CRITERIA FOR DIAGNOSING IDC VS HGPIN

- ➢ Dense cribriform glands
- ➢ Solid nests (filling the gland)
- ➢ Marked nuclear pleomorphism

ATYPICAL INTRADUCTAL PROLIFERATION

MORPHOLOGY

- A descriptive term (not an entity) ,If a lumen-spanning atypical lesion morphologically falls short of Intraductal Carcinoma, it is best to call "Atypical ductal proliferation" and recommend immediate repeat biopsy.

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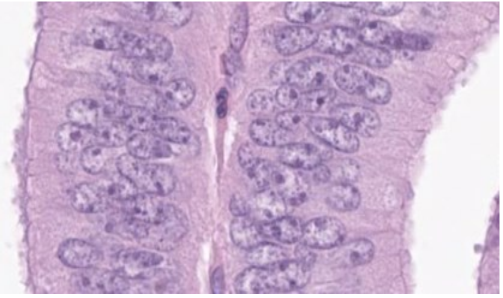
Tall, columnar, pseudostratified epithelium

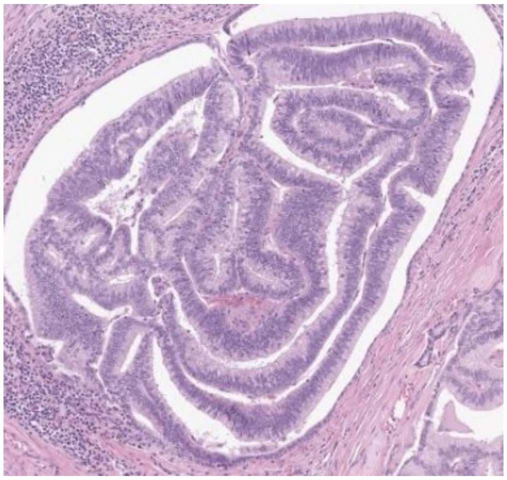


DUCTAL ADENOCARCINOMA

MORPHOLOGY

- Subtype of prostatic adenocarcinoma with **tall, columnar, pseudostratified epithelium** (looks like endometrioid adenocarcinoma of uterus)
- Typically, **periurethral location**
- Tumor cells **show elongate nuclei with cytologic atypia and amphophilic cytoplasm prominent nucleoli, and coarse chromatin**
- Abundant mitotic figure and frequent necrosis can be seen
- Combination of papillary and cribriform architecture in dilated glands
- **Similar IHC to acinar type: no basal cells, AMACR positive**
- Grade as pattern 4, if necrosis is present graded as 5

Ductal adenocarcinoma



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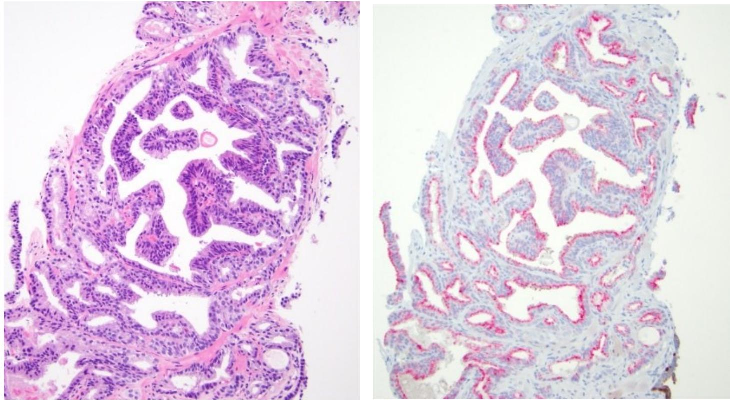
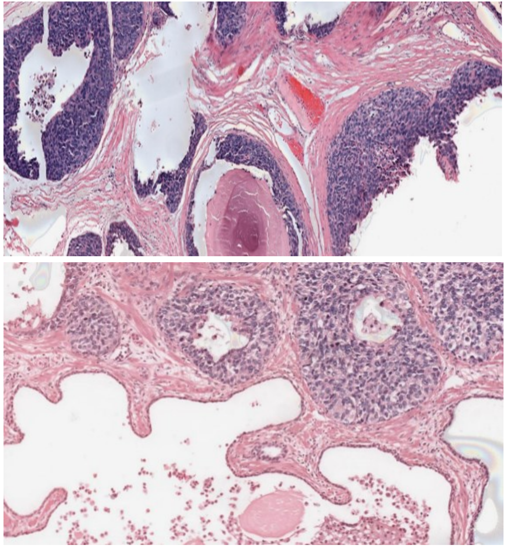
OTHER HIGH YIELD POINTS

- More likely to be mixed with acinar adenocarcinoma than to be pure
- Locally aggressive with seminal vesicle invasion and extra prostatic extension
- More aggressive than average acinar adenocarcinoma.
- More likely to have lower PSA than acinar

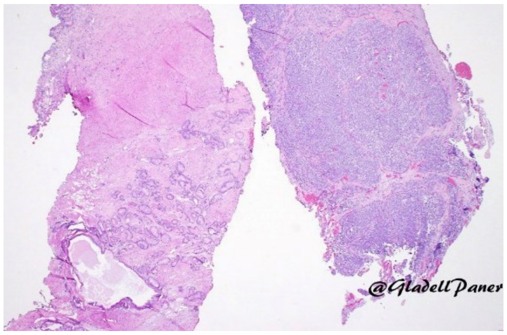


Credit: Andres Martin Acosta MD @Andres_M_Acosta

Secondary involvement of prostateby urothelial carcinoma



Prostate invovled by prostatic adenocarcinoma and urothelial carcinoma

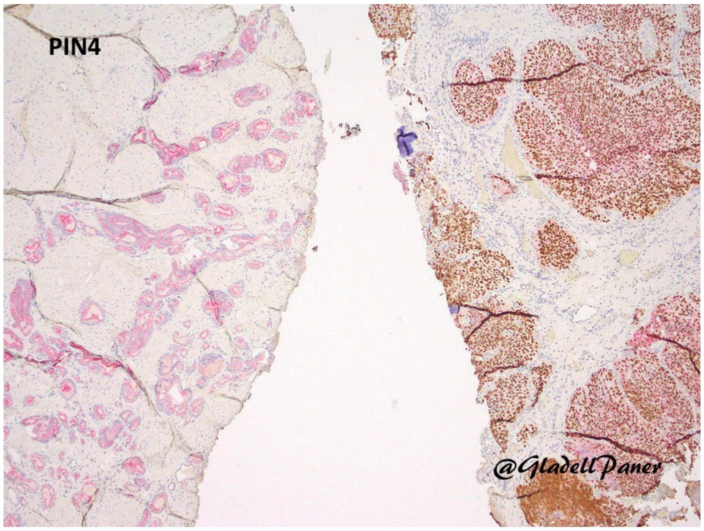


Credit: Gladell Paner, MD @GladellPaner

UROTHELIAL CARCINOMA

MORPHOLOGY

- Often **secondarily involving the prostate** from the bladder and/or prostatic urethra
- **Morphology similar to urothelial carcinoma of bladder**
- Determining the site of urothelial carcinoma is very important for staging!!
  - Bladder→ Prostate stroma =T4 (direct invasion)/T2 (mucosal)
  - Prostatic urethra→ Prostate stroma = T2
- Frequent spread of CIS or pagetoid spread into ducts
- Invasion elicits desmoplastic stroma
- **IHC: p63, HMWCK, GATA-3 (+), NKX3.1 & PSA (-)**



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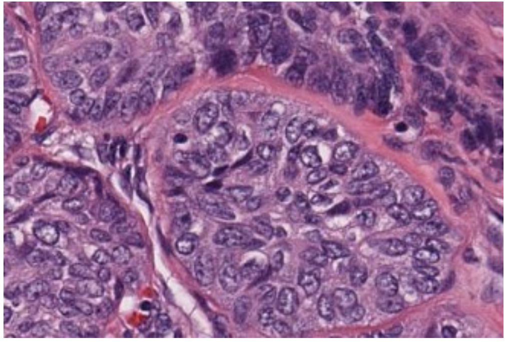
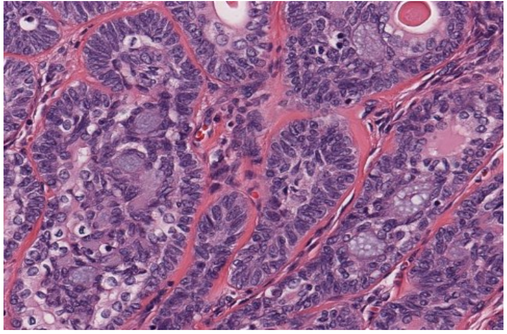
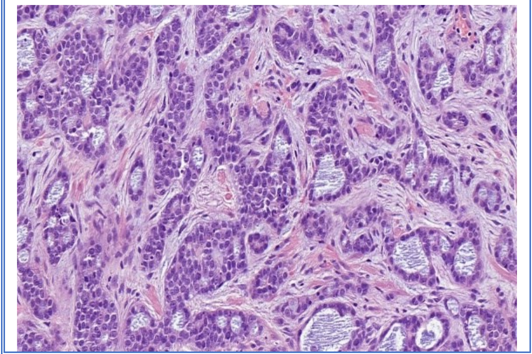
Adenoid cystic/cribriform pattern



Basaloid pattern





BASAL CELL CARCINOMA

MORPHOLOGY

- Malignant neoplasm composed of basal cells
- Uncommon
- Most cases show various proportions of following patterns
  - adenoid cystic/cribriform pattern with inspissated secretions
  - basaloid pattern with small solid nests of basal cells
- Often show desmoplastic stroma and can have hyaline rim.
- IHC: basal cell markers usually label outermost layers (sparing luminal cells), while luminal cells stain with CK7.
- HER2/neu overexpressed.
- Some cases with Adenoid cystic morphology have MYB-rearrangements (like elsewhere)

OTHER HIGH YIELD POINTS

- Normal PSA
- Usually indolent
- Aggressive behavior (large solid nests with central necrosis, high Ki67%, less staining with basal cell markers)
- Gleason grading is not recommended
- Focal squamous differentiation and clear cells are seen

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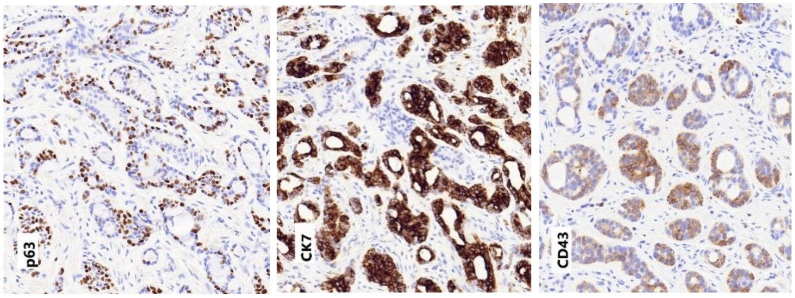
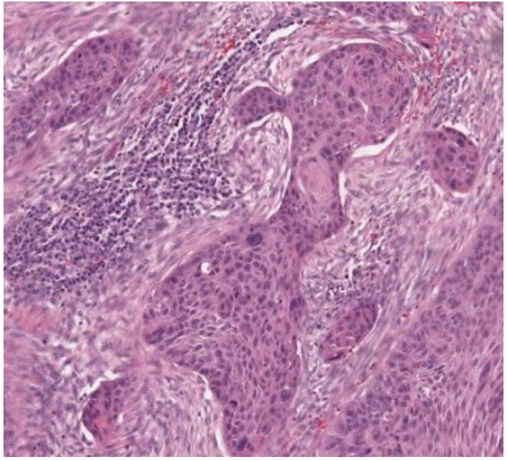
Images credit: Tristan D Rutland @TristanRutland7



P63, CK7 and CD43

Squamous cell carcinoma



SQUAMOUS CELL CARCINOMA (SCC)

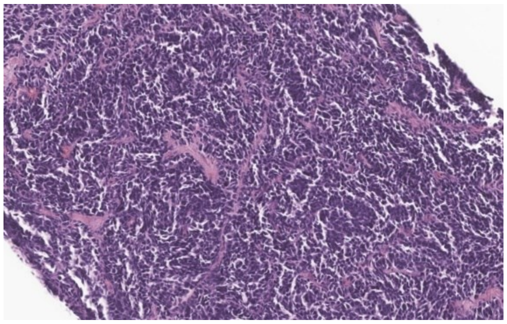
MORPHOLOGY

- **Extremely rare**
- Mostly arise through either divergent differentiation of basal cells or trans differentiation of usual adenocarcinoma **following hormone therapy**
- **Similar morphology and IHC to SCC elsewhere**
- Must be distinguished from secondary involvement of a bladder/urethral SCC or TCC.
- Adenosquamous carcinoma: **Both glandular (acinar) and squamous morphology**

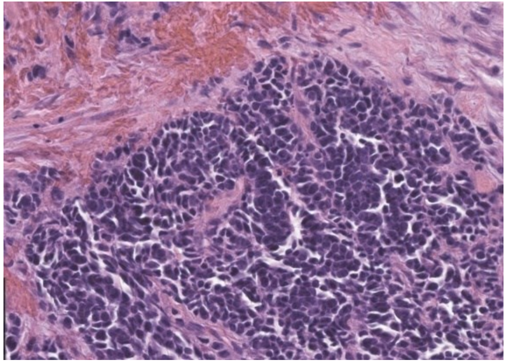
OTHER HIGH YIELD POINTS

- Criteria for diagnosis of pure primary squamous cell carcinoma of the prostate:
  - Unequivocal features of malignancy and squamous differentiation
  - No squamous cell carcinoma elsewhere

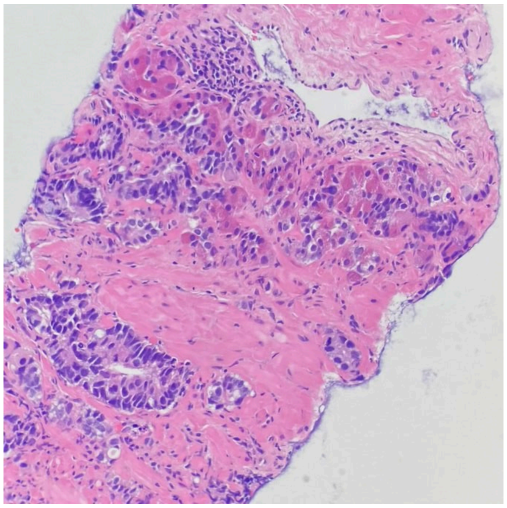
Small cell carcinoma



Small cell carcinoma: small cells with scan cytoplasm and stippled, hyperchromatic nuclei



Paneth cell-like neuroendocrine differentiation



Pranav Renavikar @RenavikarP

Path Presenter

NEUROENDOCRINE TUMORS/CARCINOMA

MORPHOLOGY

NEUROENDOCRINE TUMOR

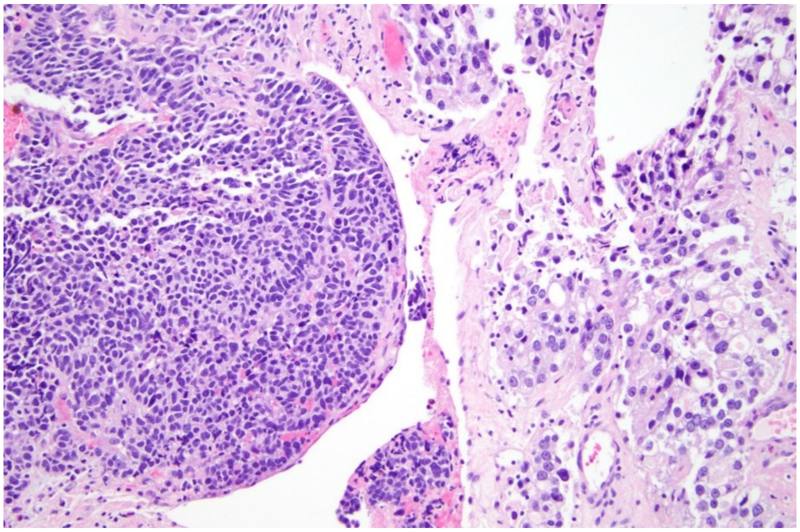
- **Well-differentiated**
- Very **rare**
- Must **exclude adenocarcinoma with neuroendocrine differentiation (with more typical areas)**

SMALL CELL NEUROENDOCRINE CARCINOMA.

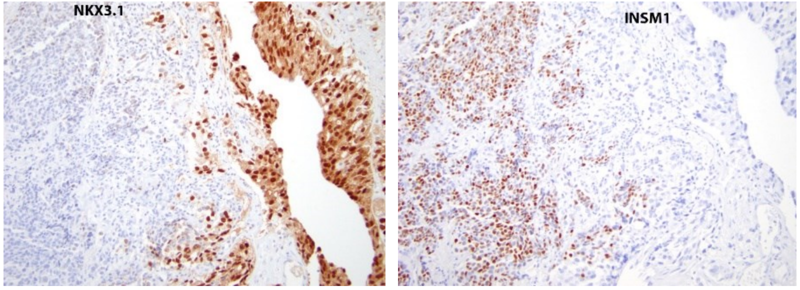
- Rarely occurs de novo
- **Usually in treated prostate cancer**
- Very **aggressive**
- Morphologically **identical to in the lung** (small cells with scan cytoplasm and stippled, hyperchromatic nuclei)
- **Necrosis in common**
- May be admixed with acinar adenocarcinoma or pure
- **Gleason grading is not recommended**
- **Stains with neuroendocrine marker usually, at least 1**

OTHER HIGH YIELD POINTS

- Neuroendocrine cells (**in some cases "Paneth cell-like neuroendocrine differentiation" can be seen on IHC in many usual prostate cancers, it is not clinically significant)**
- No routine IHC is necessary

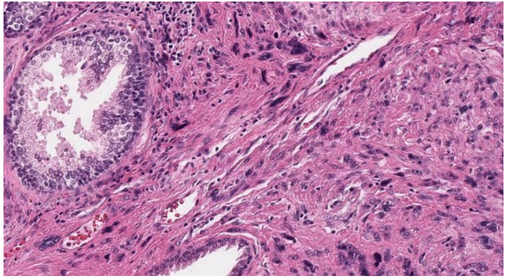


Credit: Andres Martin Acosta MD @Andres_M_Acosta

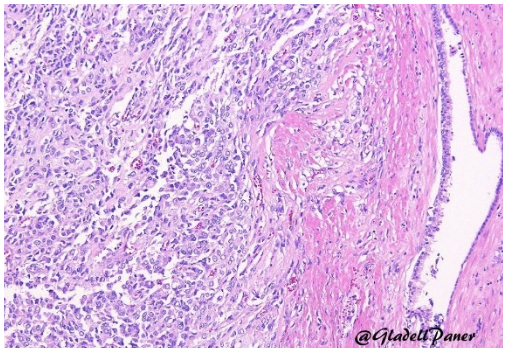


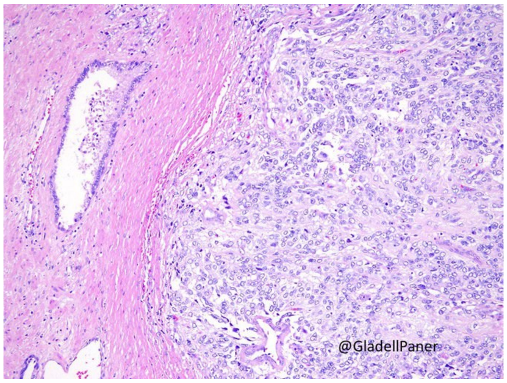
MESENCHYMAL TUMOR

STUMP: degenerative appering stromal cells and benign glands



Prostatic stromal sarcoma





- **Tumor of specialized prostatic stroma**
- All tumors like leiomyosarcoma, Rhabdomyosarcoma, Inflammatory myofibroblastic tumor, solitary fibrous tumor, GIST etc. can occur in prostatic stroma, and the morphology looks like elsewhere

STROMAL TUMOR OF UNCERTAIN MALIGNANT POTENTIAL ("STUMP")

MORPHOLOGY

- **Hypercellular stroma with scattered degenerative appearing cells and admixed with benign glands**
- Usually, good prognosis
- May recur or progress

STROMAL SARCOMA

MORPHOLOGY

- **Hypercellular stroma** with malignant appearing cells
- **Phyllodes subtype**: leaf-like branching with myxoid, epithelioid, hypercellular bland stroma
- **Aggressive**
- **IHC: Express CD34 and PR; STAT6- and CD117-**

Path Presenter

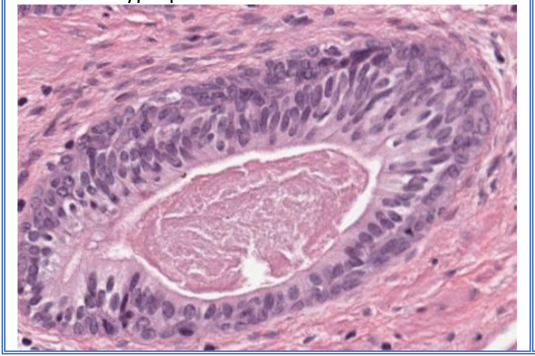
IMMUNOHISTOCHEMISTRY OF MESENCHYMAL LESIONS

	STUMP	Stromal Sarcoma	Leiomyo sarcoma	Rhabdomyo sarcoma	IMT	SFT	GIST
CD34	+	+	-	-	-	+	+
SMA	+/-	-	+	+	+	-	-
Desmin	+/-	-	+	+	-/+	-	-
Myogenin	-	-	-	+	-	-	-
CD117	-	-	-	-	-/+	-	+
ALK1	-	-	-	-	+/-	-	-
PR	+	+	+/-	-	-	+/-	-

Modified from: Epstein and Netto: Biopsy interpretation of the Prostate, 5th edition

MIMICKERS OF CANCER

Basal cell hyperplasia



BASAL CELL HYPERPLASIA

MORPHOLOGY

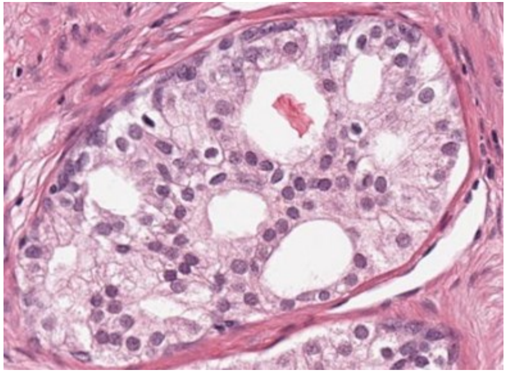
- **Proliferation of basal cells**
- **Appears blue** due to crowded nuclei with scant cytoplasm and filling tubules/glands→ may form solid nests
- Cells **lacks cytologic atypia**
- **No desmoplasia** or infiltrative growth

CENTRAL ZONE SAMPLING

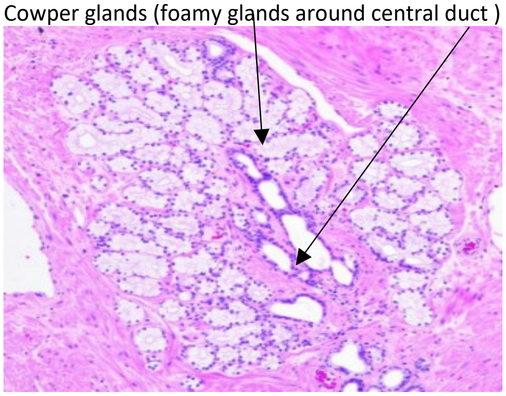
MORPHOLOGY

- **Proliferation of basal cells**
- **Appears blue** due to crowded nuclei with scant cytoplasm and filling tubules/glands→ may form solid nests.

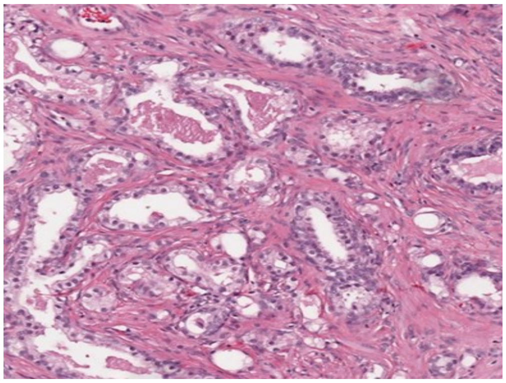
Clear cell hyperplasia, cribriform pattern



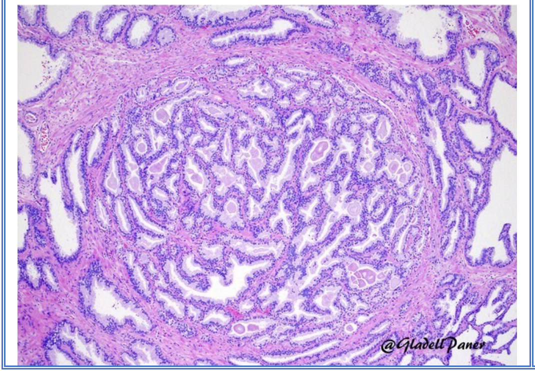
Cowper glands (foamy glands around central duct)



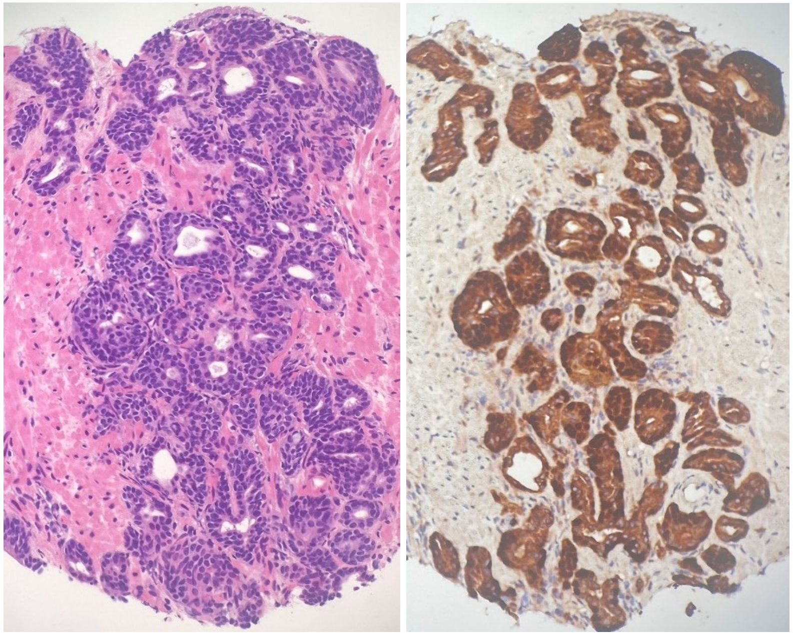
Adenosis



Adenosis



- Cells **lacks cytologic atypia**, no desmoplasia or infiltrative growth

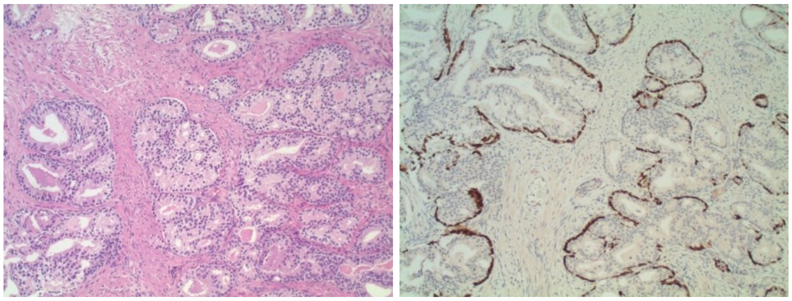


Basal cell hyperplasia H&E and PIN-4 IHC: p63: highlight basal cell ©Ankur Sangoi @slusagar

CLEAR CELL HYPERPLASIA

MORPHOLOGY

- Most often seen **in central zone on TURP in setting of BPH**
- Nodules of clear cells with smooth gland borders
- **Lobular and cribriform pattern**
- Cells show uniform bland nuclei without prominent nucleoli and **intact basal cells**



Clear cell hyperplasia: H and E and PIN4 IHC Credit: Ankur Sangoi @slusagar

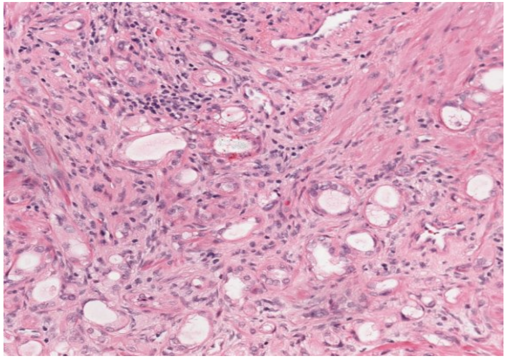
Path Presenter

COWPER'S GLANDS

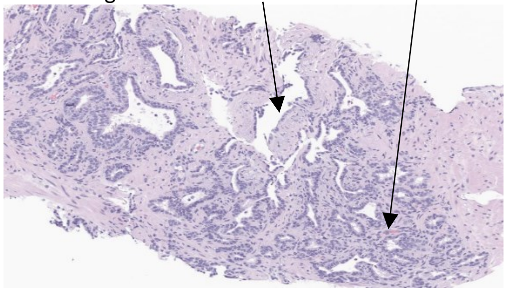
MORPHOLOGY

- Most often seen in **periurethral, near apex**
- Glands with **abundant mucin-filled cytoplasm (PASd+)**
- Lobular architecture with central duct
- **No nuclear atypia or prominent nucleoli**

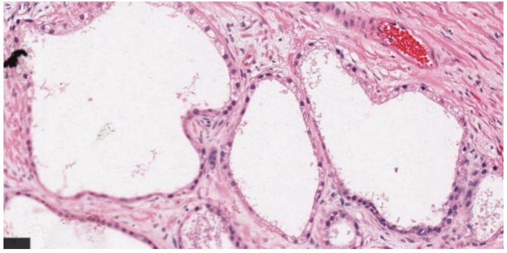
Sclerosing adenosis



Postatrophic Hyperplasia: Tightly packed glands around large dilated ducts



Partial Atrophy



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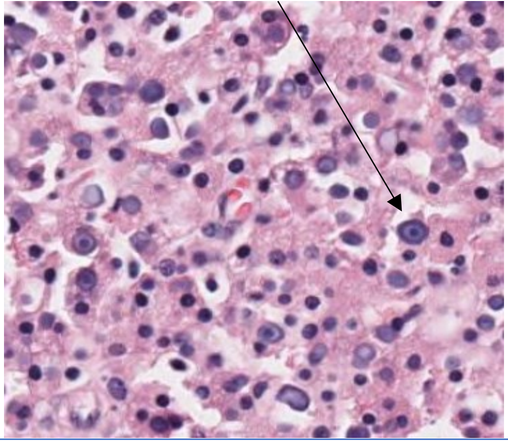
Malakoplakia: Michaelis-Gutmann bodies



- **Positive for basal cells markers and muscle specific actin**
- **IHC: PSAP negative (PSA may be positive)**

ADENOSIS/ ATYPICAL ADENOMATOUS HYPERPLASIA)

MORPHOLOGY

- Occurs in the transition zone (in TURPs and Prostatectomies)
- Well-circumscribed tightly packed, uniform glands.
- Lobular architecture with admixture of small and larger glands.
- Pale to clear cytoplasm
- Basal cells may be decreased in Adenosis

OTHER HIGH YIELD POINTS

- Some features suggestive of carcinoma may be seen such as prominent nucleoli and crystalloids/mucin, but often merge with benign glands.
- Principal differential diagnosis is carcinoma. And this distinction requires IHC for basal cells:
- Basal cells may be decreased in Adenosis
- Demonstration of any basal cells indicates adenosis in this context

[Path Presenter](#)

SCLEROSING ADENOSIS

MORPHOLOGY

- Lobular or **focally infiltrative proliferation of dense spindled stroma and entrapped epithelial elements** (small acini to cords and single cells)
- Cells and glands **lack cytologic atypia**
- Can have surrounding hyaline sheath
- **Basal cells present**
- **IHC: Positive for basal cell markers (p63, HMWCK) and express myoepithelial markers (smooth muscle actin, S100)**

[Path Presenter](#)

ATROPHY

MORPHOLOGY

SIMPLE ATROPHY :

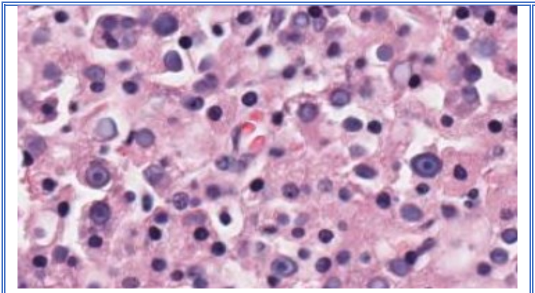
- Basophilic glands with scant cytoplasm
- Normal caliber glands with normal spacing

PARTIAL ATROPHY:

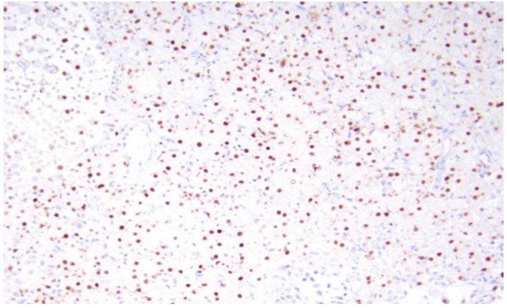
- Retain moderately abundant pale/clear cytoplasm lateral to the nuclei (with reduced apical cytoplasm), which may produce pale glands that lack the blue appearance of atrophy.
- Frequently merges with nearby atrophic glands.
- Bland nucleoli without prominent nucleoli.
- No infiltrative growth.
- Undulating luminal surfaces.
- Attenuated basal cells

POSTATROPHIC HYPERPLASIA ("PAH")

- Tightly **packed very small cytologically bland glands**
- Clustered around a larger dilated "feeder" duct (Think: TDLU of breast)
- **Bland nuclei without prominent nucleoli**
- **Basal cells present**
- Often **sclerotic stroma**



Von Kossa stain: staining calcifications



Credit: Andres Martin Acosta MD
@Andres_M_Acosta

MALAKOPLAKIA

MORPHOLOGY

- **Inflammatory condition**
- **Rare** in prostate
- Strongly associated with **infection (especially gram negative bacilli) and immunosuppression**
- **Escherichia coli and Klebsiella pneumoniae** are most common cause,
- Clinically **mimics prostatic adenocarcinoma with elevated PSA**
- Infiltration by histiocytes with eosinophilic, granular cytoplasm
- Histiocytes contain round and basophilic **intracytoplasmic inclusions** with bullseye appearance known as **Michaelis-Gutmann bodies** (pathognomonic)
- **Special stains : Von Kossa, Prussian blue highlights Michaelis-Gutmann bodies**
- **Periodic acid-Schiff (PAS) stain histiocytic**

OTHER HIGH YIELD POINTS

- Often positive urine culture for gram negative bacilli

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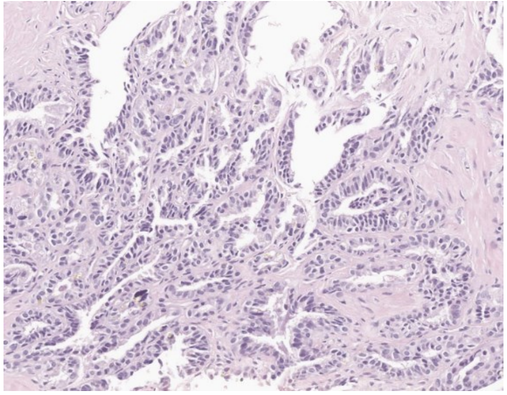
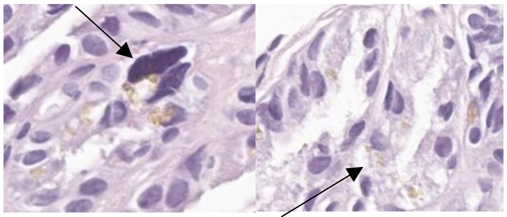
SEMINAL VESICLE

Complex invaginating ducts with papillary folds



Secretory cells pleomorphic, bizarre, hyperchromatic, and multinucleated



Lipofuscin (brown yellow refractory pigments)

SEMINAL VESICLE

MORPHOLOGY

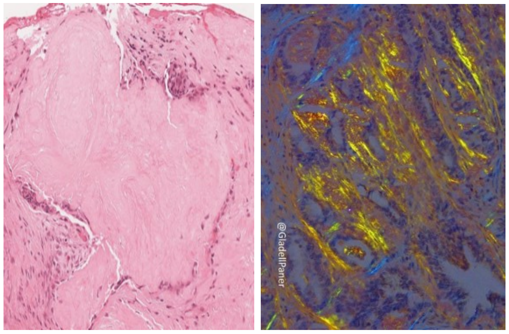
- **Paired glandular structures located in superior/posterior aspect of prostate**
- Seminal vesicle lumen/duct is **surrounded by dense smooth muscle**
- Glands show complex invaginating ducts with papillary folds surrounded by small to medium slit-like glands
- The smooth muscle wall consists of thick inner circular and thin outer longitudinal muscle layers
- The glands are lined by single layer of non-ciliated cuboidal to columnar secretory cells and underlying basal cells
- **Secretory cells show pleomorphism, bizarre atypia, hyperchromatic, and multinucleation with Lipofuscin** (brown - yellow refractory pigments) in cytoplasm
- Occasional pseudo inclusions can be present
- IHC: The glands are **CK7 and pax-2(+), and basal cells positive for basal cell marker (+)**

OTHER HIGH YIELD POINTS

- Seminal vesicle glands are CK7 positive whereas prostate glands are ck7 negative, so it can be used to differentiate in cases of seminal vesicle involvement of prostatic adenocarcinoma

Path presenter

Amorphous eosinophilic fibrillar material highlighted with Congo Red with "Apple-green" birefringence



Credit: Gladell PanerMD @GladellPaner

AMYLOIDOSIS

MORPHOLOGY

- Linear or nodular **subepithelial deposits of amorphous eosinophilic fibrillar material**
- Senile (localized) amyloid deposits seen in 4-12% of SV, incidental or on autopsy cases
- Highlighted with **Congo Red with "Apple-green" birefringence**
- Occasionally causes luminal narrowing

OTHER HIGH YIELD POINTS

- Not associated with systemic amyloidosis

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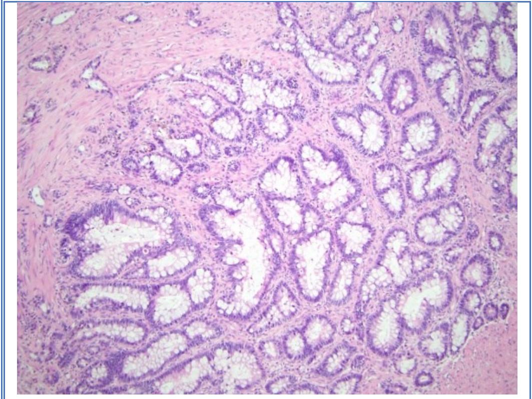
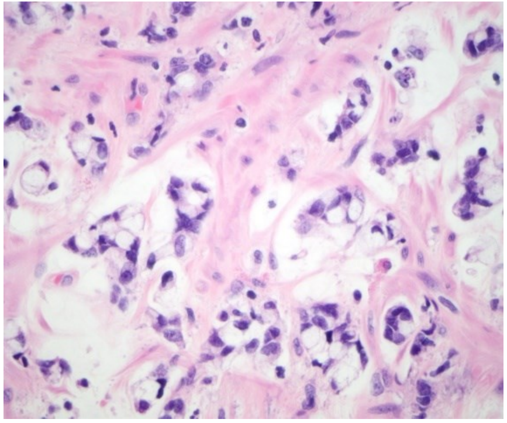


Credit: Andres Martin Acosta MD @Andres_M_Acosta



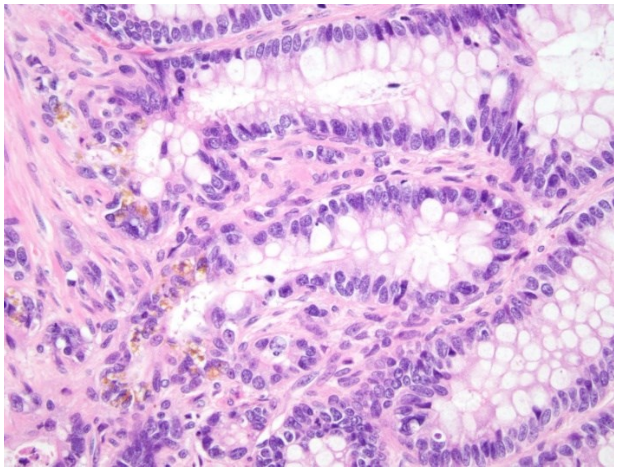
ADENOCARCINOMA

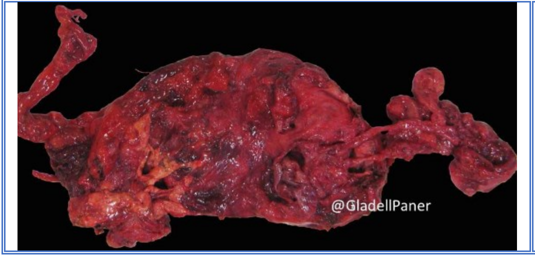
MORPHOLOGY

- Glandular or poorly differentiated tumor (solid, nested, or cord-like)
- Papillary pattern lined by columnar cells most recognized feature
- May have clear cells or hobnail morphology like clear cell adenocarcinoma in female genital tract
- Mucin production present, sometimes copious
- Carcinoma in situ may be seen, which is helpful in poorly differentiated cases
- Typically, Pax2, CA125, Ck7 positive and PSA/PAP, CK20, CDX2 negative

OTHER HIGH YIELD POINTS

- Secondary involvement of seminal vesicle considerably more common than primary adenocarcinoma (CK7 negative)
- Extremely poor



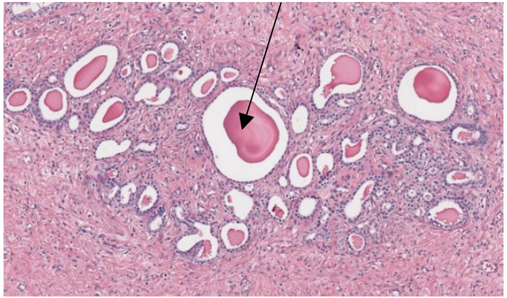


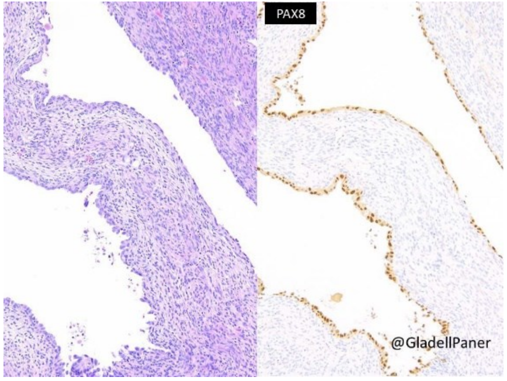
MIXED EPITHELIAL AND STROMAL TUMORS (MEST)

MORPHOLOGY

- Rare , **biphasic tumors with proliferative stromal and benign epithelial components** (like that of kidney tumor)
- **Cystic to solid masses**
- The glandular epithelium within the tumor may show lipofuscin pigment
- Cystadenoma→ Lobular pattern; Branching lumens and cysts of various sizes
- Fibroadenoma→ Spindle cell component is more pronounced.

cysts of various size and with luminal secretions.



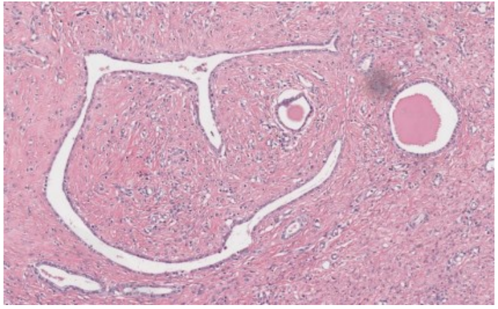


Credit: Gladell PanerMD @GladellPaner

- Adenosarcoma→ Stroma is densely cellular and condenses around distorted gland spaces (like Phyllodes- like tumors)
- **Proposed grading**
  - **Low-grade**: Cystadenoma like, no atypia, mitosis or necrosis
  - **Intermediate grade**: Increased stromal cellularity, mild atypia, rare mitosis and no necrosis
  - **High-grade**: Increased stromal cellularity, prominent atypia, increased mitosis and necrosis

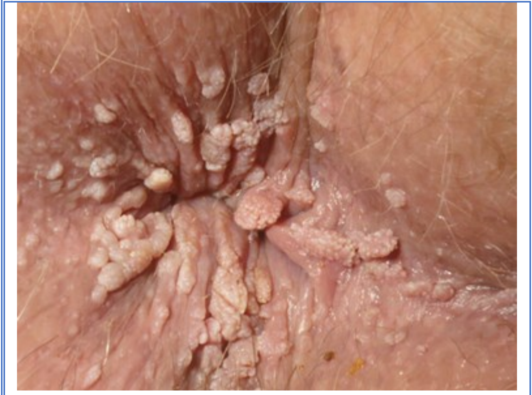
OTHER HIGH YIELD POINTS

- ~ 80% in low-grade and may recur
- A combination of stromal cellularity, atypia and mitosis might be used for the histological grading
- Glandular epithelium show negative staining for (PSA)

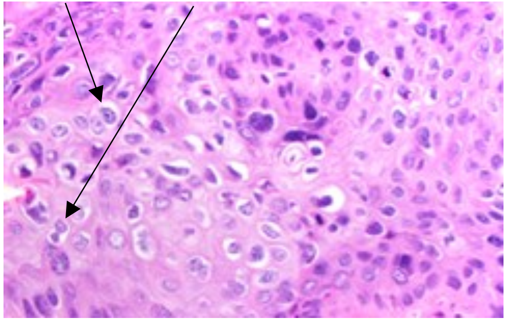


Fibroadenoma like, with more pronounced Spindle cell component.

PENIS AND SCROTUM



Koilocytes and Binucleation



CONDYLOMA ACUMINATA

MORPHOLOGY

- **Exophytic papillary fronds**
- Can be **flat or plaque-like**, white to reddish-brown in color
- Epithelium is often thickened with hyper or para keratosis
- Proliferation of large superficial hyperchromatic cells with irregular, "**Rasinoid**" nuclei and **perinuclear halos (=Koilocytes**)
- Extends no more than 1/3 thickness of the epithelium
- May **show multi or binucleation**
- **Mitoses are usually confined to lower I/3rd**
- **Can be positive for p16**

OTHER HIGH YIELD POINTS

- Often recur
- **Dysplasia due to Low-risk (85%) HPV infection**
- Common in reproductive age
- Associated with multiple sexual partners, smoking
- **Low risk of progression to cancer**
- **May regresses** spontaneously

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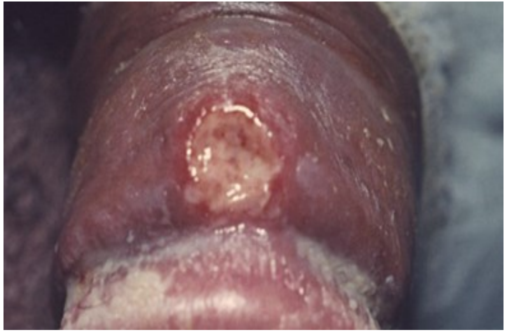
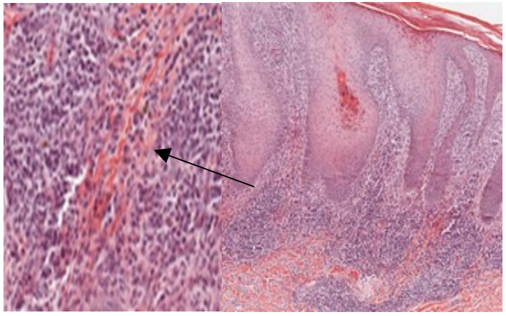
Ulcer with indurated and punched out base



Pseudoepitheliomatous hyperplasia with marked lymphoplasmacytic at the base



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SYPHILIS (PRIMARY)

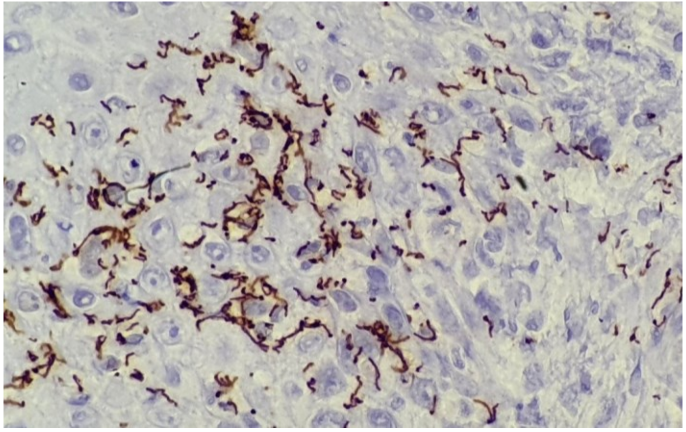
MORPHOLOGY

- Mostly in **scrotum, fore skin, shaft, coronal meatus**
- **Painless ulcer** or circumscribed red, raised, glistening lesion (chancre)
- Increased incident in homosexual males
- Multiple lesions (**HIV patients**)
- Epidermal ulceration with marked lymphoplasmacytic inflammation
- **Neutrophilic infiltrate and endothelial proliferation** can be seen
- Pseudoepitheliomatous hyperplasia at periphery of ulcer is a common finding

OTHER HIGH YIELD POINTS

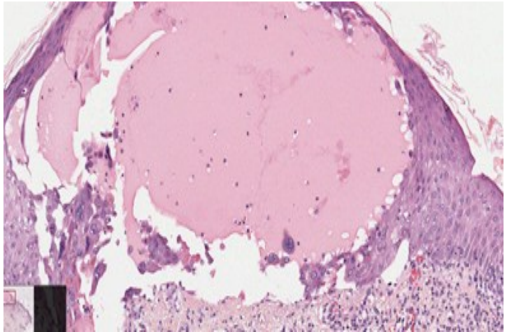
- **T. pallidum, Spirochete** (gram-negative, spiral-shaped organism)
- **Silver stain** (Warthin-Starry or Steiner) highlights the organism
- Negative stain does not exclude the diagnosis (**Rapid plasma regain/ Fluorescent treponemal antibody assay is recommended**)

T. pallidum, Spirochete (spiral-shaped organism) IHC

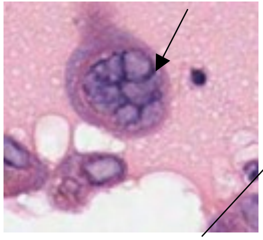


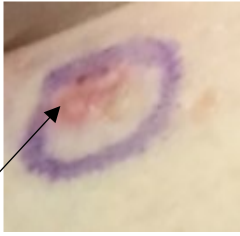
Credits: Pedro Alexio @pbaleixo MD PhD

Intraepidermal blister



Multinucleation, margination, molding





Grouped vesicles

HERPES

MORPHOLOGY

- **Grouped vesicles** (up to 3 mm)
- **Painful ulcers**
- **Intraepidermal blister**
- May have ulcerated epidermis with **pseudoepitheliomatous hyperplasia at the periphery**
- Acantholytic keratinocytes with viral inclusion (**multinucleation, margination, molding)**
- Usually prominent lymphocytic inflammatory infiltrate (**lichenoid inflammation)**
- **Lymphocytic vasculitis** may be present

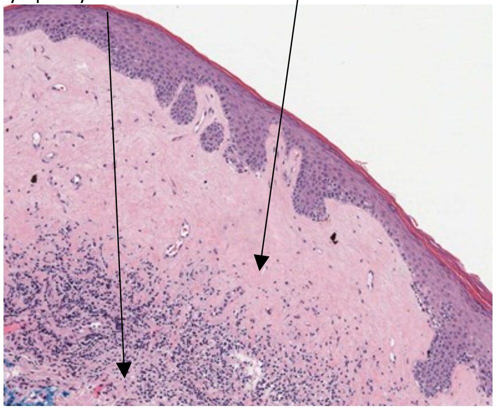
OTHER HIGH YIELD POINTS

- Herpes simplex virus (HSV) 1 or 2 (**Double-stranded enveloped DNA viruses**)
- 70-80% genital herpes are caused by HSV2
- **HSV1 and HSV2 immunohistochemistry**

Path Presenter

13. MALE GENITAL PATHOLOGY

Atrophic epithelium, hyalinized dermis with lymphocytic infiltrate beneath



LICHEN SCLEROSUS

MORPHOLOGY

- **White to red wrinkled plaques** with hypopigmentation **"tissue paper like"**
- **Affect foreskin, glans, and peri meatal region**
- **Atrophy of overlying epithelium** (loss of rete, late findings)
- Vacuolar degeneration of basal keratinocytes
- Hyalinization and edema in papillary dermis (**homogenization, late findings**)
- **Band-like lymphocytic infiltrate beneath homogenized collagen**

OTHER HIGH YIELD POINTS

- Associated with **autoimmune**
- Increased risk for **Differentiated penile intraepithelial neoplasia (PeIN**)
- Minority of cases **progress to Squamous cell carcinoma (SCC)**

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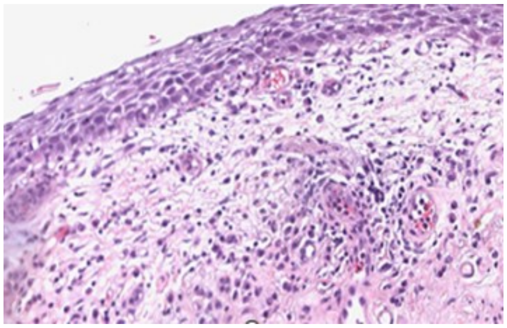
Zoon balanitis



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PLASMA CELL BALANTIS (ZOON BALANITIS)

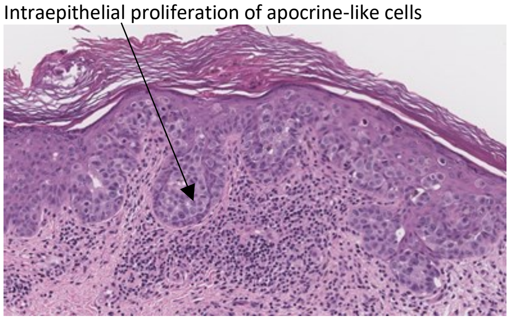
MORPHOLOGY

- **Accumulation of plasma cells** at mucosal or cutaneous sites of prepuce or glans penis (Zoon balanitis)
- **Red, erythematous, shiny plaque**
- Mild spongiosis of the epidermis
- **Lichenoid inflammation** (lymphoplasmacytic) of the dermis
- Extravasated erythrocytes, mast cells, eosinophils, neutrophils, and hemosiderin deposits are usually seen

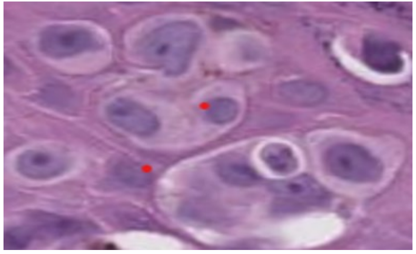
OTHER HIGH YIELD POINTS

- Usually **affects uncircumcised men**
- Treated with **corticosteroids and circumcision**
- Plasma cells are polyclonal in nature
- **Syphilis is a major differential** (ulcer, increased neutrophilic infiltrates and Spirochetes in special stain supports syphilis)

Intraepithelial proliferation of apocrine-like cells



Large cells with prominent nucleoli and pale cytoplasm



EXTRAMAMMARY PAGETS DISEASE

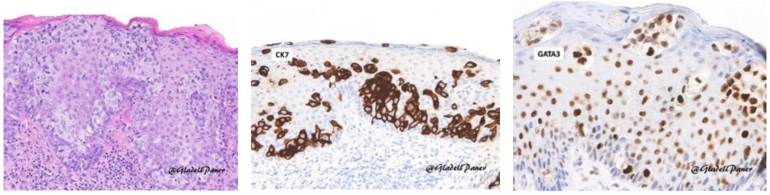
MORPHOLOGY

- **Red, erythematous plaque with sharp borders**
- Intraepithelial **proliferation of apocrine-like cells (adenocarcinoma) in groups or single cells**
- Large, round cells with prominent nucleoli and pale cytoplasm
- **Can extend down adnexal structures**

Path presenter

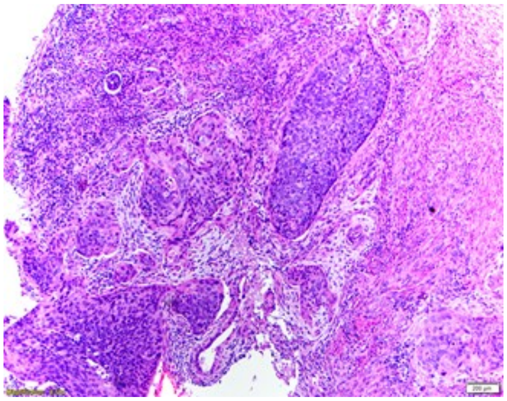
OTHER HIGH YIELD POINTS

- Usually affects **older men**
- **High rates of recurrence**
- Can **progress to invasive adenocarcinoma**.
- Important to **rule out melanoma and cutaneous pagetoid spread of urothelial or GI cancer with IHC** (see below table)



H &E, CK7, GATA 3; Credit: Gladell PanerMD @GladellPaner

	CK7	CK20	GCDFP-15	CDX2	CEA	S100 Melan A	UPK III	HER2	GATA3
PRIMARY PAGET DISEASE	+	-	+	-	+	-	-	+	+
UROTHELIAL CA	+	+	-	-	-	-	+	-	+
ANORECTAL CA	+/-	+	-	+	+	-	-	-	-
MELANOMA	-	-	-	-	-	+	-	-	-



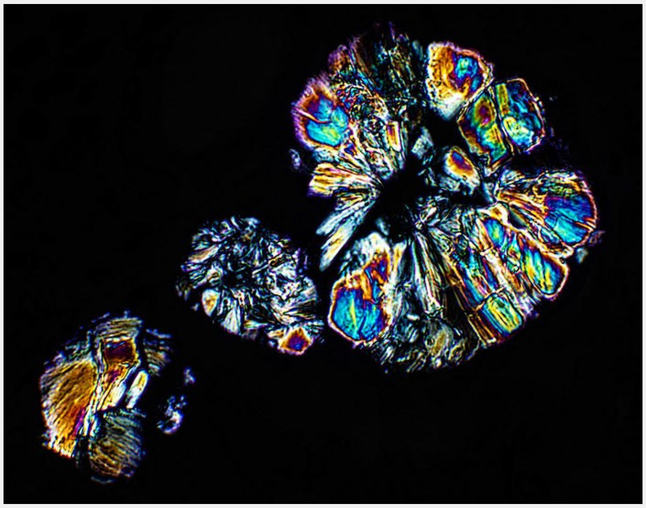
SQUAMOUS CELL CARCINOMA (SCC)

MORPHOLOGY

- **Exophytic/ indurated nodule/plaque/ non healing ulcer**
- An invasive epithelial tumor composed of squamous cells with varying degrees of differentiation.
- **Derived from HSIL** (HPV-related) or **Differentiated PIN (HPV-independent)**
- **1—25 % are associated with HPV infection**
- **Conventional (Keratinizing) SCC is most common**
- Scattered single cells with eosinophilic refractile cytoplasm
- Nuclei show marked pleomorphism, hyperchromatic and homogenous chromatin with perinuclear halo, large pleomorphic nucleoli and mitotic figures
- Necrosis is prominent with mixed inflammatory infiltrates
- keratin pearls are often present in well differentiated lesion
- Can have basaloid morphology

OTHER HIGH YIELD POINTS

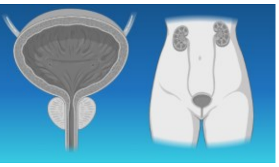
- Usually seen in **elderly**
- Risk factor: **persistent HPV infection, immunocompromised state, Lichen sclerosus**
- **Immunohistochemistry is required for poorly differentiated and spindle cell variants** (**AE1/AE3, CK5/6, P63, P40 are positive**)


Oxalate crystal in a kidney tumor. Image courtesy: Ziad El-Zaatari, MD

CHAPTER 14: UROPATHOLOGY

Swati Satturwar, MD
Snehal Sonawane, MD
Akanksha Gupta, MD

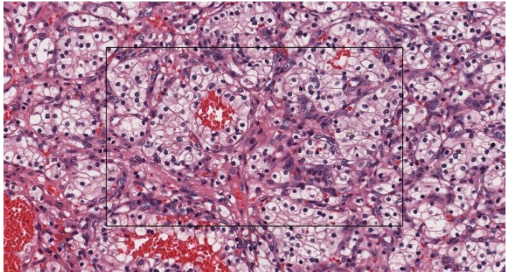
14. UROPATHOLOGY



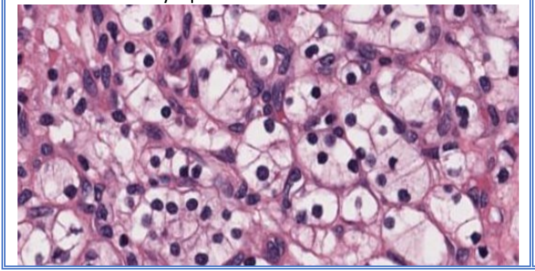
CLASSIFICATION OF KIDNEY TUMORS (WHO 2022)

OTHER TUMORS	RENAL CELL TUMORS
• Metanephric tumors	**• Clear cell tumors**
Metanephric adenoma	Clear cell renal cell carcinoma
Metanephric adenofibroma	Multilocular cystic renal neoplasm of low malignant potential
Metanephric stromal tumor	**• Papillary renal tumors**
• Mixed epithelial & stromal tumor family	Renal papillary adenoma
• Adult Renal mesenchymal tumor	Papillary renal cell carcinoma
Classic angiomyolipoma/PEComa	**• Oncocytic and chromophobe renal tumors**
Epithelioid angiomyolipoma/PEComa	Oncocytoma
Renal hemangioblastoma	Chromophobe renal cell carcinoma
Juxtaglomerular cell tumor	Other oncocytic tumors
Renomedullary interstitial tumor	**• Collecting duct renal cell carcinoma**
• Pediatric renal mesenchymal tumors	**• Other renal tumors**
Ossifying renal tumor of infancy	Clear cell papillary renal cell tumor
Congenital mesoblastic nephroma	Mucinous tubular and spindle cell carcinoma
Rhabdoid tumor of kidney	Acquired cystic disease-associated renal cell carcinoma
Clear cell sarcoma of kidney	Eosinophilic solid and cystic renal cell carcinoma
• Embryonal neoplasms of kidney	Renal cell carcinoma NOS
Nephrogenic rests	**• Molecularly defined renal carcinomas**
Pediatric cystic nephroma	TFE3-rearranged renal cell carcinomas
Cystic partially diff. nephroblastoma	TFEB- rearranged renal cell carcinomas
Nephroblastoma	ELOC (formerly TCEB1) mutated renal cell carcinoma
• Metastatic tumors	Fumarate hydratase deficient RCC
Germ cell tumors of kidney	Succinate dehydrogenase - deficient RCC
	ALK-rearranged RCCs
	SMARCB1-deficient renal medullary carcinoma

Branching vessels



Cells with clear cytoplasm



CLEAR CELL RCC

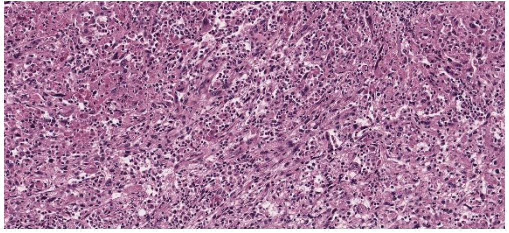
MORPHOLOGY

- Nested, tubular, or alveolar architecture, surrounded by branching capillary network, cells with optically **clear cytoplasm** (contains lipid and glycogen), +/- cysts, hemorrhage, bizarre or giant cells, rhabdoid or sarcomatoid features

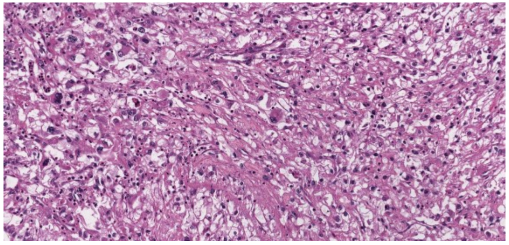
OTHER HIGH YIELD POINTS

- M: F - 2:1, typically solitary cortical tumors, most common renal ca
- Molecular: **Loss of chromosome 3p, inactivation of VHL gene, and upregulation of hypoxia-inducible factor**
- Associated with **von Hippel Lindau Syndrome (VHL gene)—**Along with Hemangioblastomas, pheochromocytoma, pancreatic serous cystadenomas, and endolymphatic sac tumor
- Multifocality, bilaterality, and early age of onset are typical of hereditary cancer syndromes such as von Hippel Lindau syndrome
- Metastasizes hematogenously to lungs, central nervous system, head and neck, and bones
- Lymphatic metastases to hilar, aortic, caval, and thoracic lymph nodes
- **Sarcomatoid transformation in 5%, poor prognosis**
- Gross: **Golden yellow +/-hemorrhage**

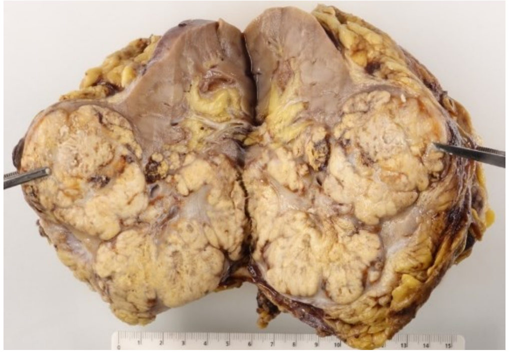
Sarcomatoid morphology



Rhabdoid, sarcomatoid, and clear cells



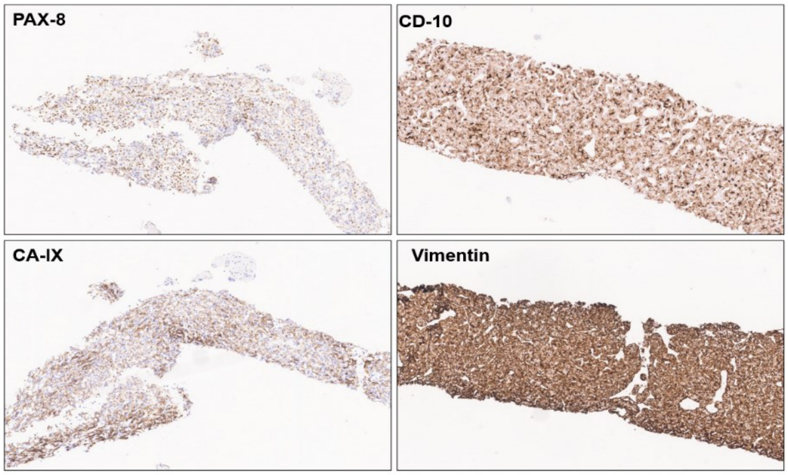
Golden yellow appearance of clear cell RCC



- FISH: Loss of 3p
- IHC: Positive: PAX8, CA IX (diffuse, membranous), RCC, Cam 5.2, EMA, CD10, vimentin; Negative: CK7, AMACR, CD117

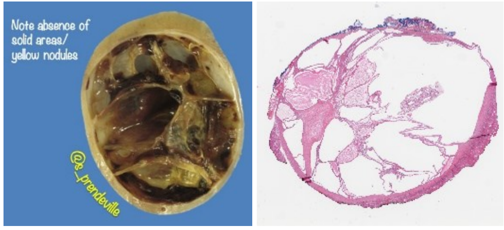
	WHO/ISUP Grading for clear cell and papillary RCC
G1	Nucleoli absent or inconspicuous & basophilic at 400x
G2	Nucleoli are conspicuous & eosinophilic at 400x and visible, not prominent at 100x
G3	Nucleoli are conspicuous and eosinophilic at 100x
G4	Any of the features like extreme nuclear pleomorphism, multinucleated giant cells, rhabdoid or sarcomatoid differentiation

Immunohistochemistry



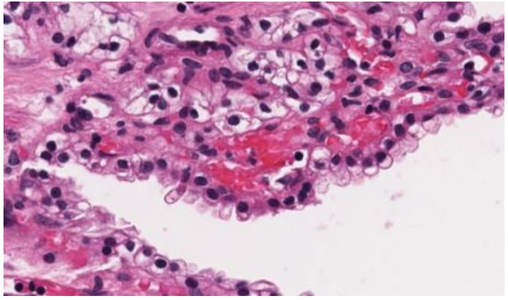
Path Presenter

Multiloculated cystic architecture



Credit: Susan Prendiville MD @S_ Prendiville

Cyst wall lined by low-grade clear cells



MULTILOCULAR CYSTIC RENAL NEOPLASM OF LOW MALIGNANT POTENTIAL

MORPHOLOGY

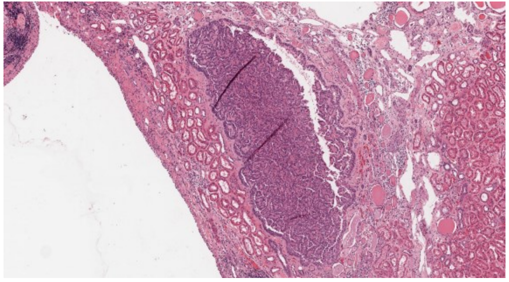
- Pure multiloculated **cystic** architecture with low grade (WHO/ISUP grade 1-2) **clear cells**
- **Should not contain any solid growth that exceeds 20x field(1mm)**
- No papillary projections, apical nuclear alignment, necrosis, atypical mitoses, LVI, rhabdoid or sarcomatoid features

OTHER HIGH YIELD POINTS

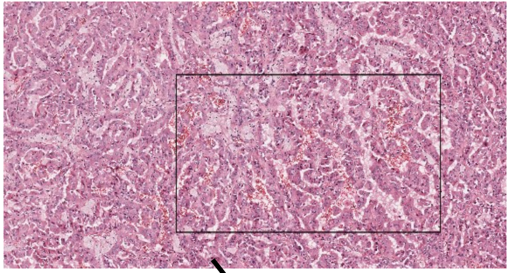
- Unilateral, solitary; Age group: 18-84 years; 1.8M:1F
- Pathogenesis: **VHL gene alterations** like clear cell RCC can be associated with VHL syndrome
- Gross: **Multiloculated variably sized cysts** with clear, gelatinous, or hemorrhagic fluid
- IHC: Positive: PAX8, CA IX (diffuse, membranous), RCC, Cam 5.2, EMA, CD10
- Negative: CK7, AMACR, CD117 • FISH: Loss of chromo 3p in 77%
- **Excellent prognosis regardless of the stage**

Path Presenter

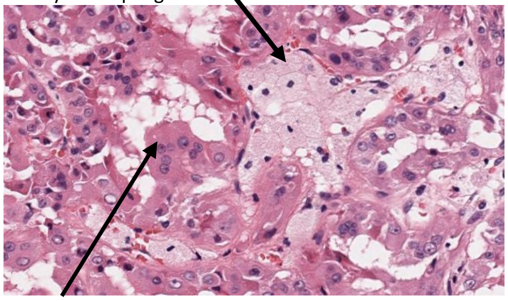
Papillary adenoma when size ≤ 1.5 cm



Tubule-papillary architecture, lined by cuboidal cells



Foamy macrophages



Cuboidal cells with abundant eosinophilic cytoplasm

[Path Presenter]

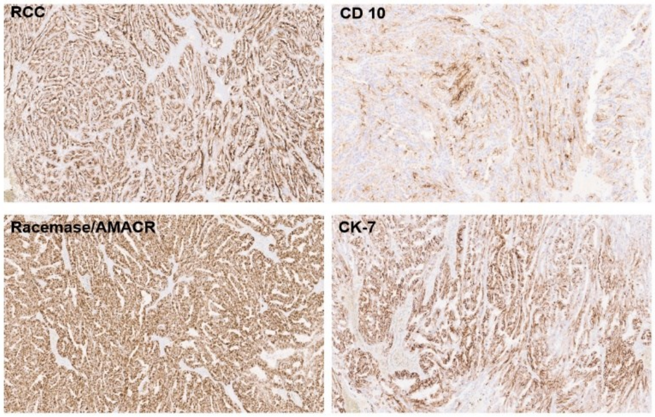
PAPILLARY RCC

MORPHOLOGY

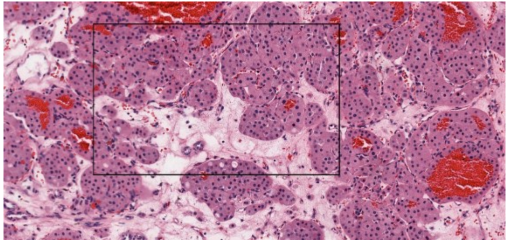
- **Papillary or tubule-papillary architecture**, lined by cuboidal cells (**low-grade** tumors); cells can have abundant basophilic, eosinophilic, clear +/- cytoplasm, hemosiderin pigment
- **Do not require foamy macrophages or psammoma bodies** for diagnosis
- There should not be too much architectural pattern heterogeneity
- Nuclear grading similar to clear cell RCC

OTHER HIGH YIELD POINTS

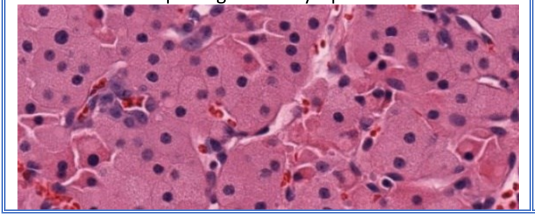
- Subclassification to type 1 and type 2 is not recommended
- **If the size is <1.5 cm, it is papillary adenoma**
- More common in chronic renal disease or acquired cystic disease in adults, uni or multifocal
- Pathogenesis: **Gains of chromosome 7, 17 and loss of Y chromosome**, MET gene germline mutations in hereditary cases
- Gross: Variegated, hemorrhage, necrosis, granular or friable due to papillary structures
- Differential diagnosis of high-grade PRCC: FH deficient RCC, eosinophilic solid-cystic RCC, Collecting duct ca, tubulocystic RCC
- IHC: Positive: PAX8, CK7 (but negative in eosinophilic tumors), AMACR, vimentin, CD10, FH; Negative: CAIX (can be focal positive)
- Immunohistochemical stains



Solid nests of oncocytic tumor cells



Abundant eosinophilic granular cytoplasm



ONCOCYTOMA

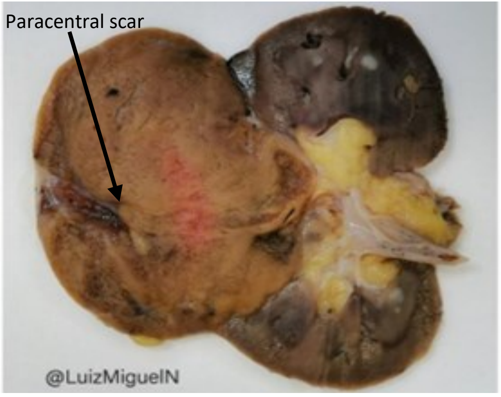
MORPHOLOGY

- Solid nests, tubules, or microcysts of oncocytic tumor cells
- Abundant **eosinophilic granular cytoplasm** (**mitochondria** on EM), **round eccentric nuclei with prominent nucleoli**
- Hypocellular hyalinized or myxoid stroma. No mitosis or necrosis
- Should **not** have a perinuclear halo or raisinoid nuclei

OTHER HIGH YIELD POINTS

- Renal cortex, benign; Age: 32-89 years, 2M: 1F, stellate scar on imaging, rarely multiple. Arise from intercalated cells of distal tubules
- Rare hereditary cases in Birt-Hogg-Dube syndrome with hybrid tumor
- Pathogenesis: **Recurrent losses of 1,14,21, X, Y**, subset shows CCND1 rearrangements, mutations of mitochondrial genes
- Gross: **Mahogany brown to a yellow-tan well-circumscribed tumor**, **central or paracentral stellate scar**

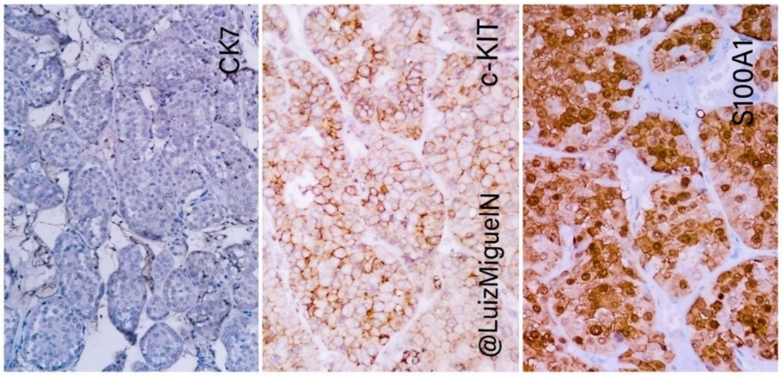
Gross Photograph: Image credits: @LuizMiguelN



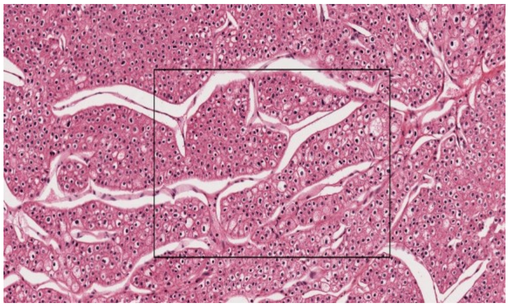
[Path Presenter]

- IHC: Positive: CK7 (scattered single cells or -), CD117, S100A, E-cadherin, AE1/3; Negative: Vimentin, CAIX,
- Differential diagnosis: Chromophobe RCC, SDH deficient RCC

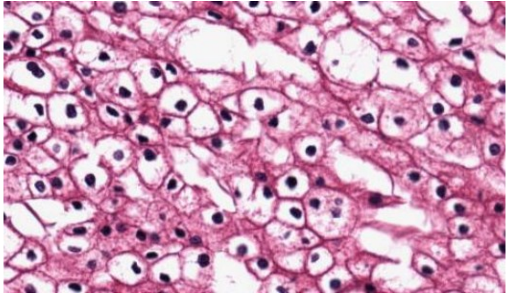
Immunohistochemical stains:



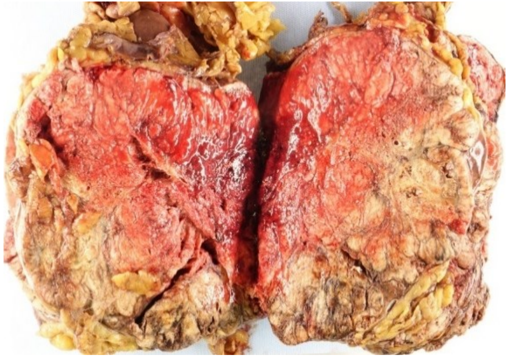
Nests of cells



Cells with clear to eosinophilic cytoplasm with prominent cell membrane, wrinkled nuclei with perinuclear halo.



Gross photograph



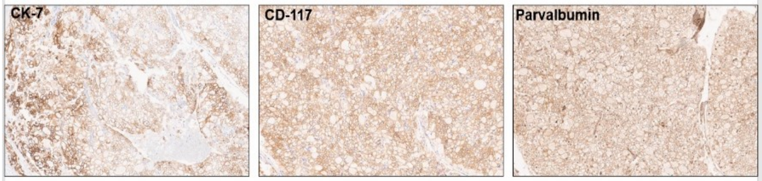
CHROMOPHOBE RCC

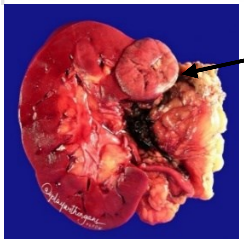
MORPHOLOGY

- Solid sheets, nests, trabecular, alveolar, microcystic pattern, pale cells with **clear or eosinophilic cytoplasm** with a **prominent cell membrane**, hyperchromatic **raisinoid** /wrinkled nuclei with characteristic **perinuclear halo**
- Hyalinized vascular stroma
- Sarcomatoid change 2-8%
- Histologic grading is not recommended

OTHER HIGH YIELD POINTS

- Location: Renal cortex; Age: 17-92 years, M= F
- Hereditary: **Birt-Hogg-Dube syndrome, Cowden syndrome**
- Pathogenesis: **Recurrent losses of 1,2,6, 10, 13, 17 ,21, Y, mutations of mitochondrial genes**
- Gross: **Gray or light-tan, central scar 15%**
- EM: Cytoplasmic microvesicles (clear cells), mitochondria (eosinophilic cells)
- Hybrid oncocytoma-chromophobe tumors in Birt-Hogg-Dube syndrome
- Differential diagnosis: Oncocytic renal carcinoma, NOS, translocation RCC, oncocytic angiomyolipoma
- IHC: Positive: CK7 (diffuse), CD117, parvalbumin, AE1/3, Hale's colloidal iron; Negative: Vimentin, CAIX, CD10

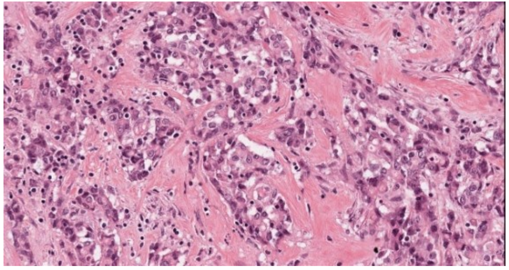




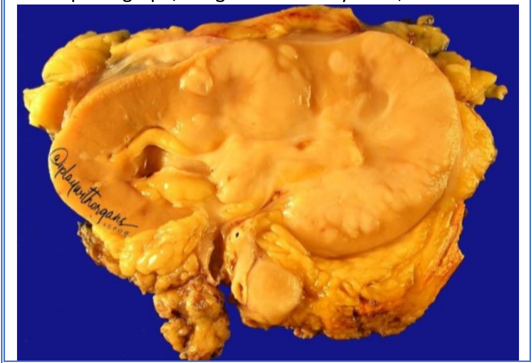
Gray or light-tan, central scar

[Path Presenter]

Infiltrating tubular architecture surrounded by desmoplastic stroma



Gross photograph, image credits: Cory Nash, MD



COLLECTING DUCT CARCINOMA

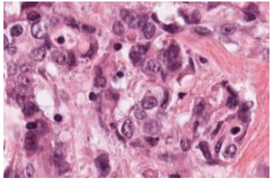
MORPHOLOGY

- Predominantly **infiltrating tubular architecture** surrounded by **desmoplastic stroma** with **high-grade cytology**
- Necrosis, mitoses (atypical forms)
- Prominent inflammation around tumor +/- mucin

OTHER HIGH YIELD POINTS

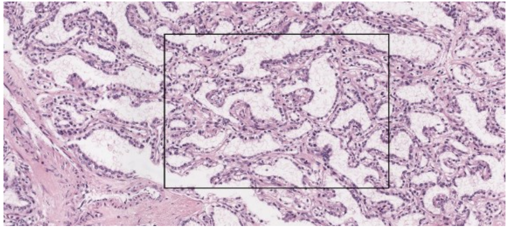
- Rare <1%, age range: 13-87 years, 2M:1F
- Location: **Medulla of kidney**
- Pathogenesis: Complex chromosomal aberrations, CDKN2A loss, NF2, and SETD2 mutations
- Gross: Gray white +/- hemorrhage, necrosis
- Differential diagnosis: **Need to exclude other RCCs, urothelial ca, or metastasis**
- IHC: Positive: HMWCK (CK19, 34BE12), CK7, PAX8, SMARCB1, FH Negative: GATA3

High-grade cytology

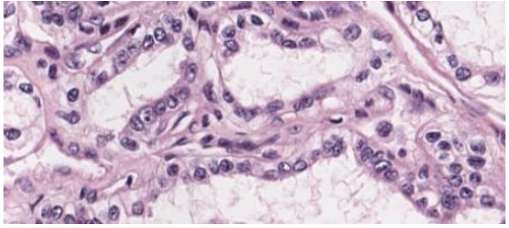


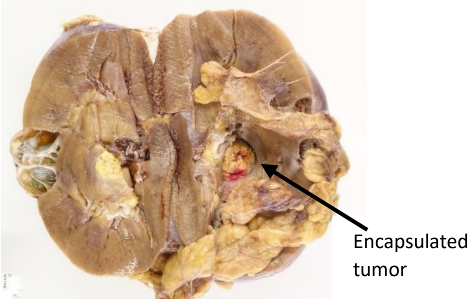
Path Presenter

Tubules, cysts



Apical location of nuclei away from basement membrane creating a piano-key appearance





CLEAR CELL PAPILLARY RENAL CELL TUMOR (CCPRCT)

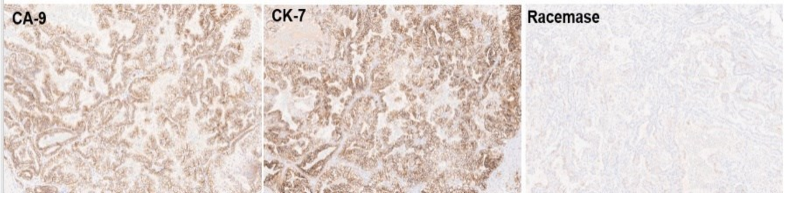
MORPHOLOGY

- Tubules, cysts, papillae, small nests of clear cells, fibrous stroma
- Grade 1-2 nuclei, **apical location of nuclei away from basement membrane creating a piano-key appearance**

OTHER HIGH YIELD POINTS

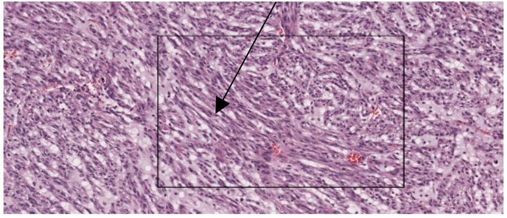
- Age range: 8-88 years, associated with ESRD, 20-25% multifocal, bilateral
- Usually, small <4cm
- Pathogenesis: unknown; **lacks chromosome 3p loss or VHL gene alterations** seen in clear cell RCC
- Gross: **encapsulated, cystic; >95% pT1**
- IHC: Positive: **CK7** (diffuse), **CAIX (cup-shaped),** GATA3, PAX8, HMWCK (34BE12); Negative: AMACR, CD10
- Differential diagnosis: Clear cell RCC, papillary RCC

Immunohistochemical stains

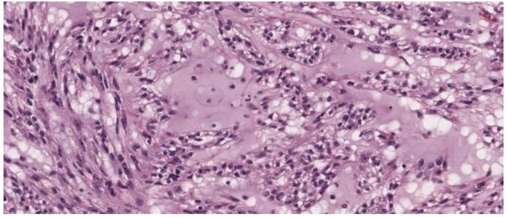


Path Presenter

Anastomosing tubules lined by cuboidal cells



Spindled cells and myxoid matrix



MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

MORPHOLOGY

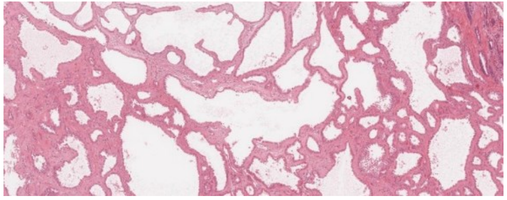
- Tightly packed, **anastomosing tubules lined by low-grade cuboidal cells** merged with **spindled cells** and **myxoid matrix**

OTHER HIGH YIELD POINTS

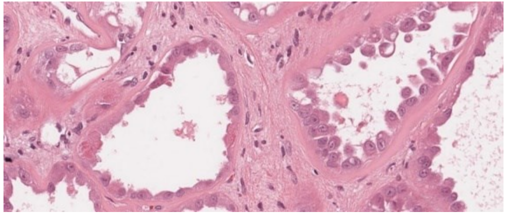
- Rare, 1M:3-4F, age range: 13-84 years
- Pathogenesis: **Multiple chromosomal losses** 1,4,6,8,9,13,14,15,22
- Gross: Solid, gray-white with a yellow cut surface
- High-grade transformation occurs in a subset with high-grade nuclei, necrosis, and mitoses, sarcomatoid transformation
- IHC:
  Positive: PAX8, CK7, AMACR, CD10 (rare)
- Differential diagnosis: Papillary RCC

Path Presenter

Tubulocystic morphology



Cyst lined by Hobnail, cuboidal, flattened cells



TUBULOCYSTIC RCC

MORPHOLOGY

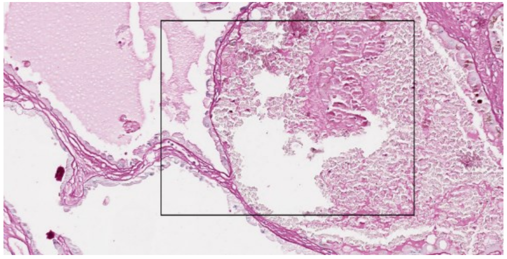
- Pure **tubulocystic morphology**, fibrotic stroma
- **Hobnail, cuboidal, or flattened cells**

OTHER HIGH YIELD POINTS

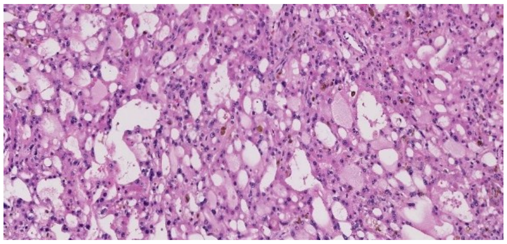
- Rare, cortex or corticomedullary junction, Left>Right
- Age range: 30-74 years, M>F
- Pathogenesis: **Gain of chromosome 17, losses of 9 and Y**
- Gross: **Cystic, bubble wrap appearance**
- **Good prognosis**
- DD: Other tubulocystic tumors of the kidney

Path Presenter

Cystic architecture



Sieve like structures



ACQUIRED CYSTIC DISEASE ASSOCIATED RCC

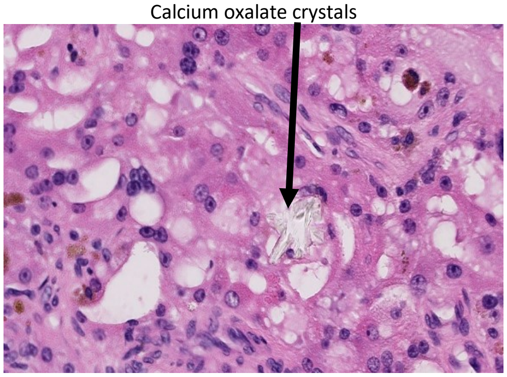
MORPHOLOGY

- Sieve-like, papillary, tubular, microcystic, or solid architecture
- Tumor cells with intracytoplasmic lumina imparting sieve-like appearance, **intra-tumoral oxalate crystals**

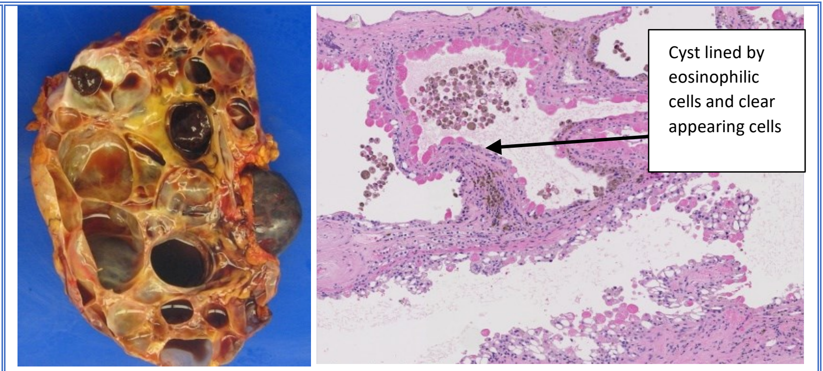
OTHER HIGH YIELD POINTS

- Often **multiple and bilateral**, it exclusively **affects patients with ESRD on long-term dialysis**
- Pathogenesis: oxalate accumulation, uremia, oxidative stress
- Gross: Yellow tan
- IHC: Positive: PAX8, CD10, RCC, AMACR; Negative: CK7, CD117, GATA3

Path Presenter

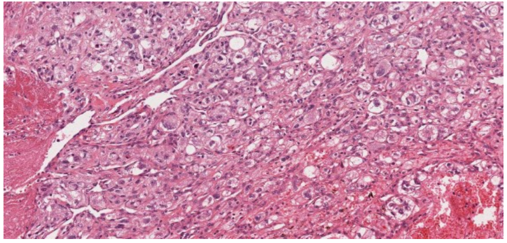


Calcium oxalate crystals

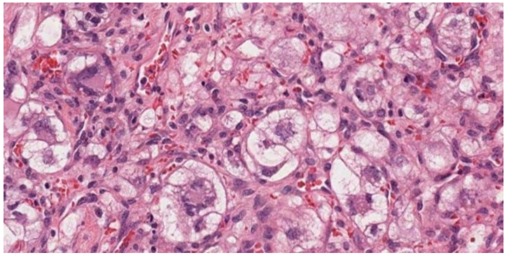


Credit: Snehal Sonawane MD @snehalshankar

Solid and cystic, tubular architecture



Oncocytic cells with abundant eosinophilic cytoplasm vacuolation, multinucleation



EOSINOPHILIC SOLID CYSTIC RCC

MORPHOLOGY

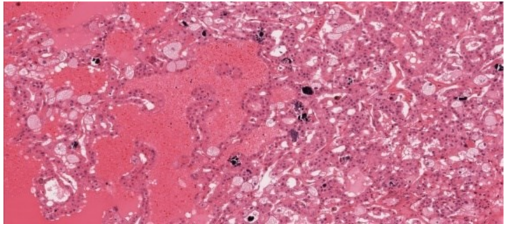
- Solid and cystic, tubular architecture lined by **oncocytic cells** with abundant eosinophilic cytoplasm with **basophilic cytoplasmic stippling, vacuolation, multinucleation**
- Variable foamy histiocytes, lymphocytes, psammoma bodies

OTHER HIGH YIELD POINTS

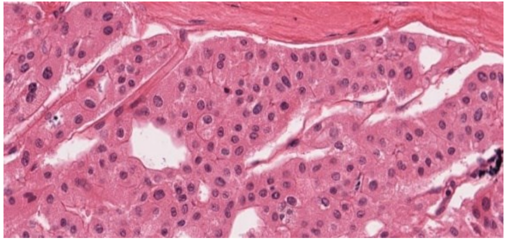
- Age range: 14-75 years
- Pathogenesis: **Mutations in TSC1 or TSC2 in the majority, upregulation of mTOR pathway**
- Gross: Tan, solid-cystic cut surface
- IHC: Positive: PAX8, CK20 (diffuse or focal), CK7 (focal) Cathepsin K, Negative: CD117,
- Differential diagnosis**:** Chromophobe RCC, translocation RCC

Path Presenter

Mixed architectural patterns with psammoma bodies



Epithelioid cells with eosinophilic cytoplasm



TFE3 REARRANGED RCC/Xp11 translocation RCC

MORPHOLOGY

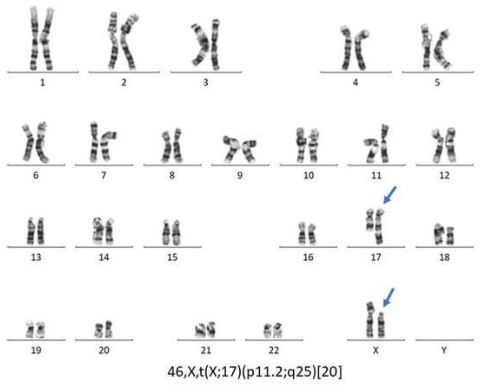
- Mixed architectural patterns, **papillary architecture with psammoma bodies, epithelioid cells with clear to eosinophilic cytoplasm**

OTHER HIGH YIELD POINTS

- Account for 40% of pediatric and 4% of adult RCCs
- Pathogenesis: Exposure to chemotherapy, **TFE3 gene (X11p) rearrangements** with multiple partners like ASPSCR1, PRCC, and others detected by FISH
- Gross: Not specific
- IHC: Positive: PAX8, TFF3**,** Cathepsin K, Melanocytic markers (HMB45, MelanA); **Negative: CKs, EMA**
- Differential diagnosis: PEComa, papillary RCC

Path Presenter

G-banded analysis of TFE3 rearranged RCC



Credits: Yassmine Akkari, Ph.D. @akkari_yassmine

TFEB REAARNGED RCC t (6,11)

MORPHOLOGY

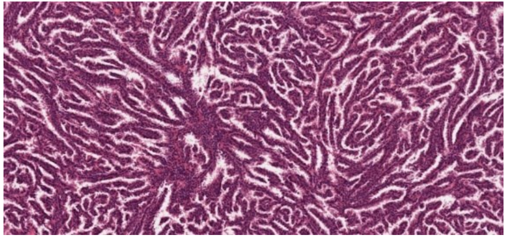
- **Biphasic with nests of larger epithelioid cells and smaller cells surrounding basement membrane material**

OTHER HIGH YIELD POINTS

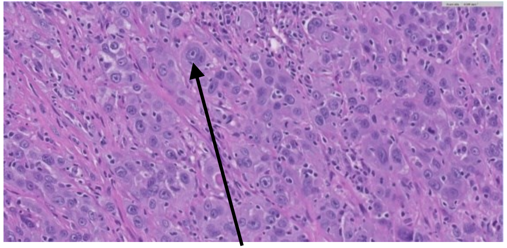
- Median age: 31 years
- Pathogenesis: **TFEB gene fusion or amplification, t(6,11),** FISH shows TFEB rearrangement
- Gross: not specific
- IHC: Positive: PAX8**,** TFFB**,** Cathepsin K, Melanocytic markers (HMB45, MelanA); **Negative: CKs, EMA**
- Differential diagnosis: Papillary RCC

Path Presenter

Papillary architectural pattern



Solid architectural pattern



Cells with macro nucleoli

FUMARATE HYDRATASE(FH) DEFICIENT RCC

MORPHOLOGY

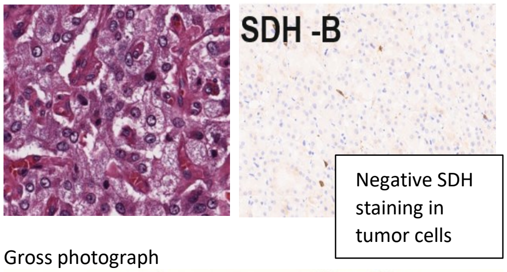
- Mixed architectural patterns like papillary, solid, tubulocystic, cystic, or sieve-like
- **Cells with at least focal eosinophilic macronucleoli**

OTHER HIGH YIELD POINTS

- Median age: 44 years; 1.9M:1F
- Familial cases: **Hereditary leiomyomatosis and RCC (HLRCC) syndrome associated RCC; history of skin and uterine leiomyomas**
- Pathogenesis: Germline or somatic mutations of the **FH gene** (chromosome 1q), FH is involved in Kreb cycle
- Gross: Tan, solid, solid-cystic cut surface
- IHC: **Positive: PAX8, 2SC ; Negative: FH**
- Differential diagnosis: High-grade papillary RCC, collecting duct ca, RCC NOS
- Genetic testing for familial cases recommended

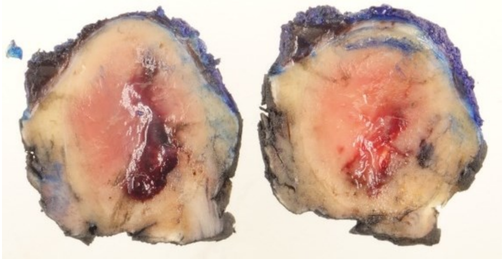
Path Presenter

Solid sheets of eosinophilic cells



Negative SDH staining in tumor cells

Gross photograph



SDH DEFICIENT RCC

MORPHOLOGY

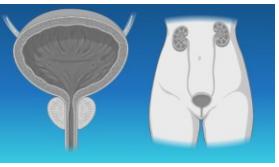
- **Solid sheets of eosinophilic cells** with occasional flocculent **cytoplasmic inclusions**
- The cytoplasm is not granular like oncocytoma
- Rare high-grade transformation with necrosis, mitosis

OTHER HIGH YIELD POINTS

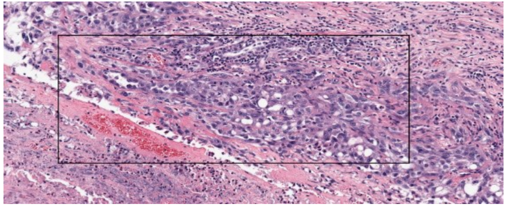
- Age range: 14-76 years
- **Multifocal, bilateral in 30%**
- Pathogenesis: Inactivation of any one of **SDH genes** due to **germline mutation**
- Gross: Tan-brown, solid cut surface
- Good prognosis
- IHC: Positive: PAX8**,** FH; **Negative**: **SDH,** CD117, CK7
- Differential diagnosis: Chromophobe RCC
- Genetic counseling and testing for germline mutation of SDH

Path Presenter

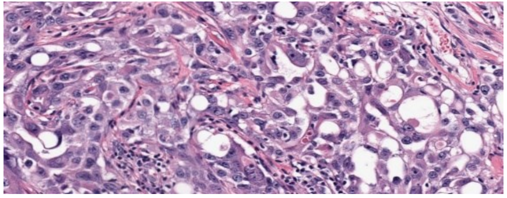
14. UROPATHOLOGY



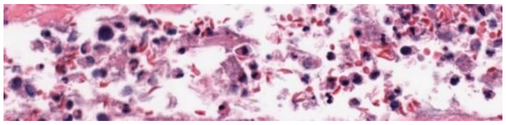
Infiltrating sheets, cords, solid nests,



High-grade cells



Sickled RBCs



SMARCB1 DEFICIENT RENAL MEDULLARY CARCINOMA

MORPHOLOGY

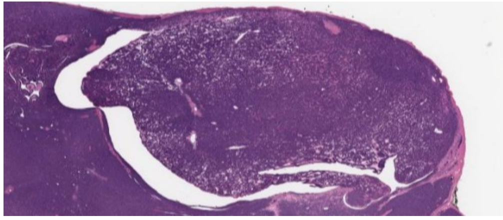
- Infiltrating sheets, cords, solid nests, microcysts, tubules of **high-grade cells, rhabdoid-like cells**
- **Myxoid desmoplastic stroma,** chronic inflammation
- **Sickled RBCs**

OTHER HIGH YIELD POINTS

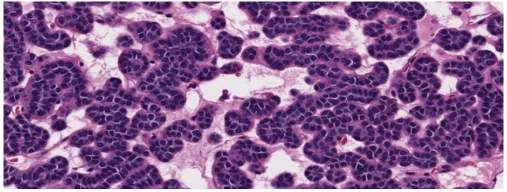
- Age range: childhood to 7th decade, **location medulla**
- **Associated with sickle cell trait>disease**
- Pathogenesis: Sickle cell-mediated hypoxic injury to the medulla, SMARCB1 gene inactivation at chromosome 11q by deletion or translocation
- Gross: Gray white with necrosis on the cut surface
- EM: Long microvilli, desmosomes
- **Poor prognosis**
- IHC: Positive: PAX8, CK, EMA, Vimentin, CK7, HMWCK, CEA, p53, OCT 3/4 (50%); Negative: SMARCB1 (INI1)
- Differential diagnosis: Collecting duct ca, RCC NOS

Path Presenter

Basophilic well-circumscribed nodule



Small primitive tubules without lumens



METANEPHRIC ADENOMA

MORPHOLOGY

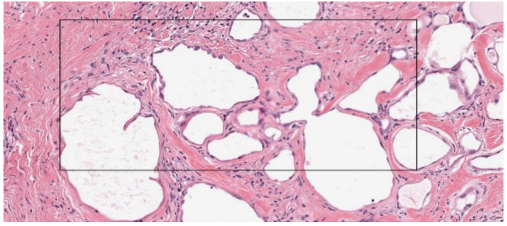
- **Small primitive tubules without lumens, minimal stroma, NO MITOSIS**
- +/- papillary or Glomeruloid architecture
- Basophilic well-circumscribed nodule on low magnification

OTHER HIGH YIELD POINTS

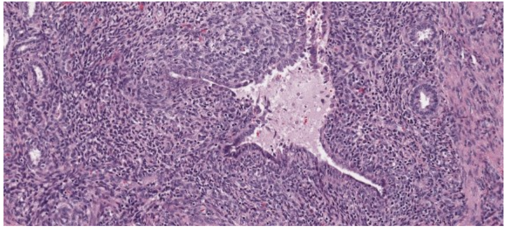
- An incidental benign lesion, 50-60 years;2 F:1M
- Pathogenesis: **BRAF mutation in 90% of cases**
- Gross: Tan nodule, well-circumscribed
- **Good prognosis**
- IHC: Positive: **PAX8, WT1, CD57, BRAF**; Negative: CK7, AMACR, EMA, CD56
- Differential diagnosis**:** Papillary RCC, Nephroblastoma

Path Presenter

Cystic nephroma



MEST: epithelial elements embedded in the stroma



MIXED EPITHELIAL AND STROMAL TUMOR OF KIDNEY

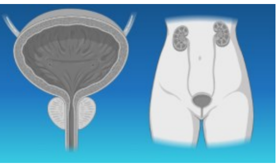
MORPHOLOGY (CYSTIC NEPHROMA AND MEST)

- Cystic nephroma: Multilocular cystic tumor lined by **flat, cuboidal, hobnail cells** and separated by **benign spindle cells resembling ovarian stroma**
- MEST: **Solid**-cystic tumor, epithelial elements in a variably cellular stroma

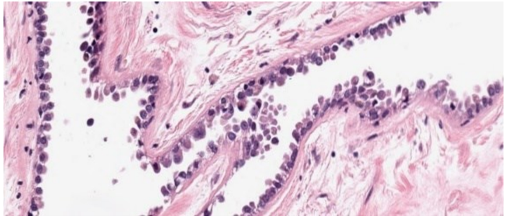
OTHER HIGH YIELD POINTS

- Middle-aged women; 7F:1M; **renal medulla**
- Pathogenesis: Hormonal imbalance, Abnormalities of chromosomes 8, 11, 17; **NO DICER1 mutation**, unlike pediatric cystic nephroma
- The spectrum contains cystic nephroma and MEST
- Gross: Cystic nephroma: Entirely cystic, MEST: Solid-cystic
- **Good prognosis**, rare cases of malignant sarcomatoid transformation
- IHC: Positive: Epithelial cells: PAX8, Stromal cells: Actin, Desmin, CD10, ER, PR, inhibin, calretinin: Negative: Cathepsin K

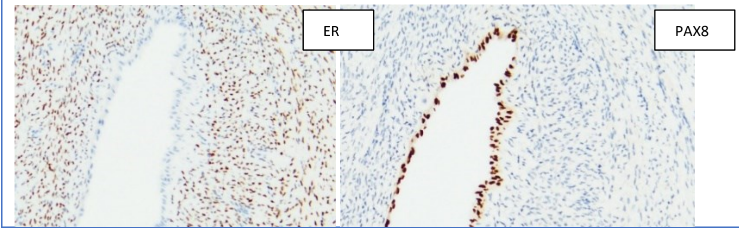
Path Presenter



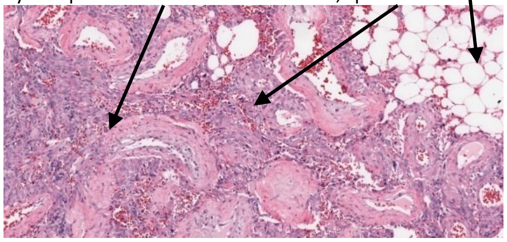
Cystic tumor lined by cuboidal, hobnail cells



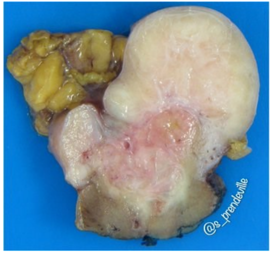
- Immunohistochemical stains:



Classic triphasic appearance mature adipose tissue, dysmorphic thick-walled blood vessels, spindle cells



Gross photograph



[Path Presenter]

Image credit: Susan Prendiville MD @S_ Prendiville

CLASSIC ANGIOMYOLIPOMA/PEComa OF KIDNEY

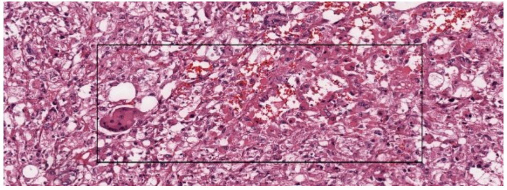
MORPHOLOGY

- Classic triphasic, **myoid spindle cells**, **mature adipose tissue**, and **dysmorphic thick-walled blood vessels** without elastic lamina
- Smooth muscle component: can be hypercellular, atypical, or pleomorphic +/- hemorrhage

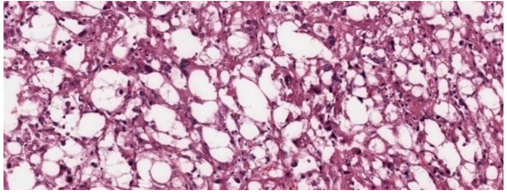
OTHER HIGH YIELD POINTS

- Peak 5th decade; 4F:1M**;** CT: Fat-containing tumor
- Pathogenesis: a proliferation of perivascular epithelioid cells hence the name PEComa, **TSC2 or TSC1 inactivation**
- Syndromic association with tuberous sclerosis: Can be multifocal
- Gross: Unencapsulated, appearance depends on the proportion of different components
- **Good prognosis as classic tumors are benign**
- IHC: Positive: **Co-expression of smooth muscle and melanocytic markers** (SMA, MSA, Calponin, HMB45, MelanA, ER, PR, S1OO) Negative: CK, PAX8, CAIX, GATA3, Inhibin
- Differential diagnosis: Clear cell RCC, Liposarcoma, leiomyoma, leiomyosarcoma, melanoma, adrenal cortical tumors

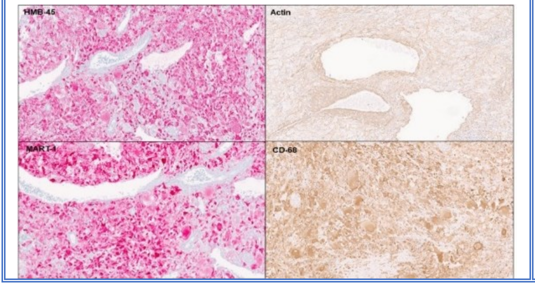
Nests of atypical large eosinophilic ganglion-like cells



Lipomatous areas



Immunohistochemical stains



EPITHELIOID ANGIOMYOLIPOMA/EPITHELIOID PEComa OF KIDNEY

MORPHOLOGY

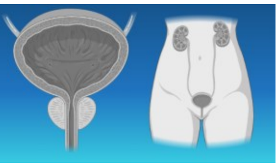
- It should contain at least **80% epithelioid cells**
- Carcinoma-like pattern: Nests of atypical **large eosinophilic ganglion-like cells** or diffuse sheets of epithelioid and spindle cells (cells with voluminous cytoplasm)
- Multinucleated giant cells, lipomatous areas +/- thick vessels

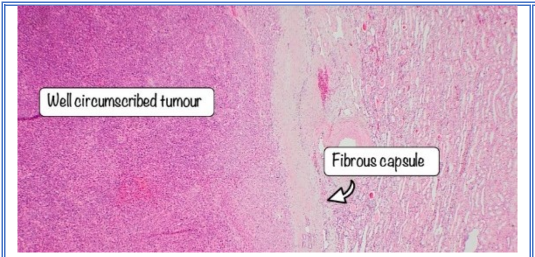
OTHER HIGH YIELD POINTS

- Peak 5th decade; M=F; CT: May show fat-containing tumor
- Pathogenesis: a proliferation of perivascular epithelioid cells hence the name PEComa, **TSC2 mutation in sporadic cases**
- Syndromic association with tuberous sclerosis in which can be multifocal
- Gross**:** Large, unencapsulated, heterogenous appearance depends on the proportion of different components
- **Lymph node or renal vein involvement is common, rare cases of malignant transformation** (Criteria: >70% atypical epithelioid cells, mitosis ≥2/10hpf, atypical mitotic figures, necrosis)
- IHC: Positive: Expression of melanocytic markers: HMB45, MelanA, MITF; Cathepsin K; variable expression of smooth muscle markers, TFE3 in a subset of cases; Negative: CK, PAX8, CAIX, GATA3, Inhibin
- Differential diagnosis: Carcinomas, metastatic tumors, sarcoma

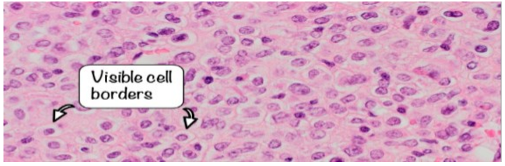
[Path Presenter]

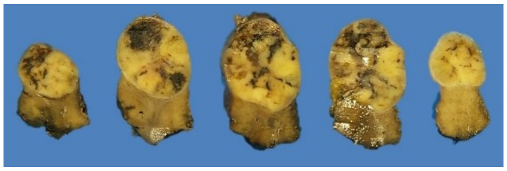
14. UROPATHOLOGY





Round to polygonal cells





Credit: Susan Prendiville MD @S_ Prendiville

JUXTAGLOMERULAR CELL TUMOR

MORPHOLOGY

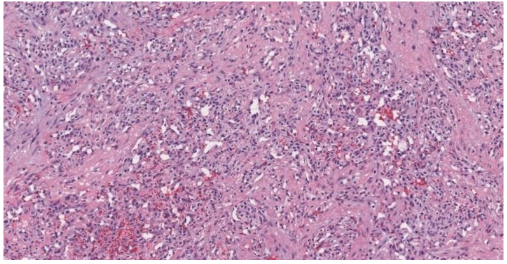
- Solid sheets or lobules of round to **polygonal to spindle cells** with prominent vasculature, variable cytologic atypia, hyalinized vessels
- Mitosis is not seen
- Tumor giant cells entrapped renal tubules at the periphery

OTHER HIGH YIELD POINTS

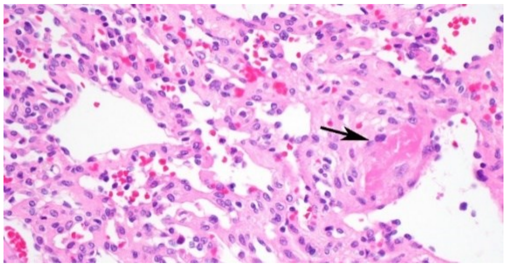
- Benign, rare, **young- adults**; F>M
- Pathogenesis: Alterations like gains of chromosome 19, losses of chromosome 9 and X
- Rare cases with metastasis
- Gross: well-circumscribed tumor, tan cut surface, usually solid, may have a cystic component
- **Good prognosis**
- EM: **Characteristic rhomboid crystals, renin granules**
- IHC: Positive: **Renin, PAS, CD34**, Vimentin, +/- CD117
  Negative: CK, PAX8, RCC, synaptophysin, chromogranin, HMB45, desmin

Path Presenter

Non-lobular architecture, anastomosing proliferation of capillary sized vessels



Hobnail endothelial cells and fibrin thrombi



Credit:Andres Martin Acosta MD @Andres_M_Acosta

ANASTOMOSING HEMANGIOMA

MORPHOLOGY

- Non-lobular architecture, an **anastomosing proliferation of capillary-sized vessels**, reminiscent of splenic sinusoids, within a framework of non-endothelial supporting cells
- Hobnail endothelial lining cells, and fibrin thrombi are typical
- No to rare mitosis
- Extramedullary hematopoiesis and mature fat in 50%

OTHER HIGH YIELD POINTS

- Type of capillary hemangioma that simulates angiosarcoma
- Locations: kidney, urinary bladder, testis
- Pathogenesis: **GNA14 and GNAQ mutations**
- Gross: Well-circumscribed with hemorrhagic areas
- Differential diagnosis: Angiosarcoma (marked atypia)
- IHC: Positive: CD31, CD34, ERG, SMA (supporting cells)
- Negative: D2-40

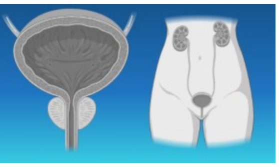
Path Presenter

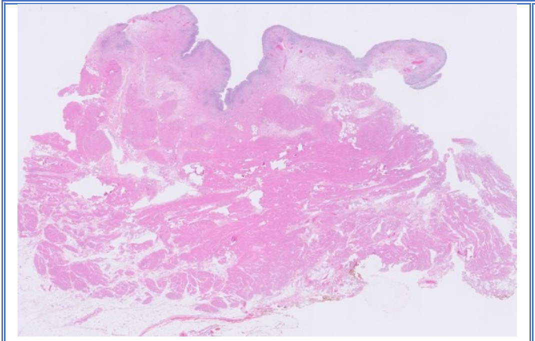
URINARY BLADDER: NON-NEOPLASTIC

NORMAL HISTOLOGY

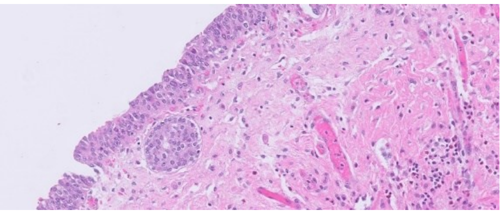
- The normal urothelium is **5-7 layers thick**
- The bottom layer of basal cells, variable layers of intermediate cells, and topmost layer of umbrella cells
- Beneath epithelium is lamina propria containing small lymphatics, wispy muscularis mucosae
- Detrusor muscle/muscularis propria
- Perivesical adipose tissue

14. UROPATHOLOGY

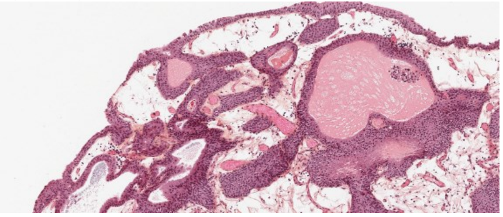




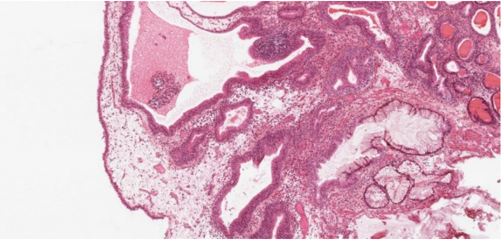
Von Brunn nests



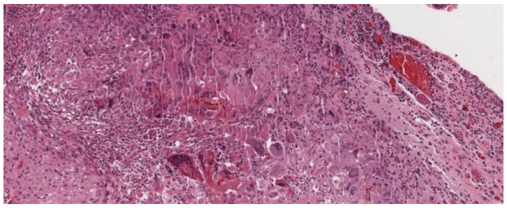
Cystitis cystica



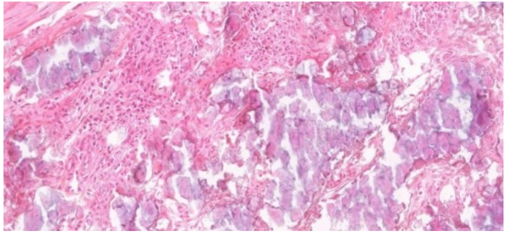
Cystitis glandularis



Prior TURBT site change with foreign body giant cells and inflammation



Precipitation of salts (encrusted cystitis)



VON BRUNN NESTS

- Most common proliferative change
- **Invaginations of the surface urothelium,** present in bladder and ureters
- No atypia, regular size/shape
- If florid **can mimic a nested type of invasive urothelial cancer**

CYSTITIS

CYSTITIS CYSTICA AND CYSTITIS GLANDULARIS

- Cystoscopy: Cysts/nodular lesions
- A reactive process in response to irritation, infection, injury, mostly involves trigone and bladder neck
- **Von Brunn nests with cystic dilation+/- secretions (cystitis cystica)** and with cystic dilation with a formation of a gland-like lumen and lined by intestinal-type epithelium or glandular metaplasia (**Cystitis cystica et glandularis**)
- May regress

FOLLICULAR CYSTITIS

- Children> adults
- Cystoscopy: Pinpoint white lesions
- **Lymphoid follicles with germinal centers** within lamina propria

PAPILLARY OR POLYPOID CYSTITIS

- Reactive process, **associated with indwelling catheters**
- Cystoscopy: Polypoid mucosa/papillary
- Edematous, **broad fibrovascular cores**, non-branching papillae lined by normal or reactive urothelium

INTERSTITIAL CYSTITIS

- **>6 weeks** of unpleasant sensation, associated with **lower urinary tract symptoms** in the absence of infection or identifiable cause
- Cystoscopy: **Hunner ulcers** in late stages
- Non-ulcerative or ulcerative +/- **mast cells**

GRANULOMATOUS CYSTITIS

- Due to **BCG therapy**, **mycobacterial infections**, **fungal infections** (candida, aspergillus)
- Necrotizing and non-necrotizing granulomas
- Differential: Prior biopsy site change with granulomatous reaction

ENCRUSTED CYSTITIS

- **Precipitation of salts** leading to the encrustation of the bladder mucosa in alkaline urine, related to urea splitting bacteria, F>M
- **Calcified debris embedded in the mucosa** and on the surface

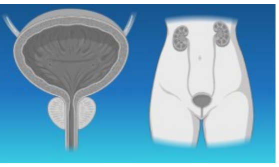
EMPHYSEMATOUS CYSTITIS

- Pneumatosis of the bladder due to **trauma, fistula, instrumentation or urinary stasis, UTI (E. coli)**
- Cystoscopy: Air bubbles under the mucosa
- Pneumatosis of the bladder with **air bubbles surrounded by foreign body giant cell reaction**

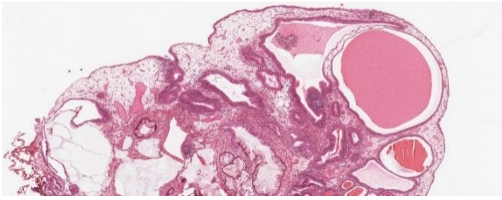
Link Link Link Link

Path Presenter

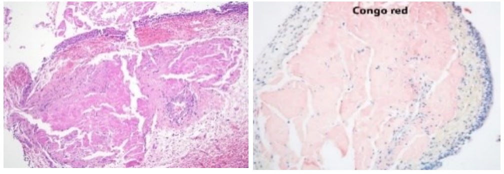
14. UROPATHOLOGY



Emphysematous cystitis

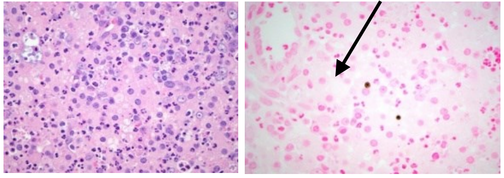


Amyloidosis of urinary bladder



Malakoplakia of urinary bladder

Foamy macrphages Michaelis-Gutmann bodies



Credit:Andres Martin Acosta MD @Andres_M_Acosta

AMYLOIDOSIS OF URINARY BLADDER

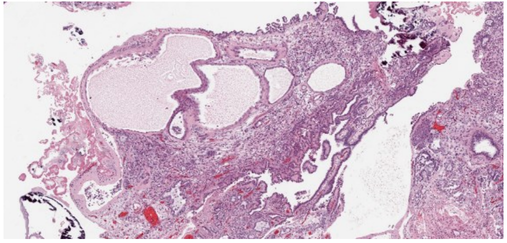
- Primary amyloidosis of the urinary bladder is rare.
- Presents as painless hematuria
- Cystoscopy: may mimic bladder cancer; **yellowish submucosal plaques**
- Microscopy: eosinophilic amorphous deposits around the vessels and in the lamina propria

MALAKOPLAKIA OF URINARY BLADDER

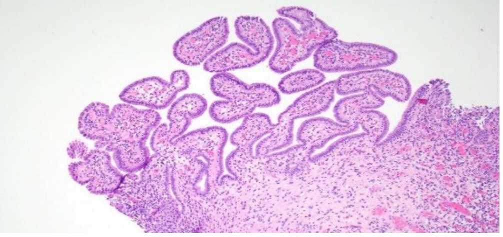
- A rare inflammatory condition typically affects the urinary tract common in immunocompromised patients
- **E. coli is the most common etiology**
- Microscopy shows foamy macrophages, chronic inflammation, and **calcified Michaelis-Gutmann bodies** (von Kossa stain)

Path Presenter

Papillary and tubulocystic nephrogenic metaplasia



Papillary nephrogenic adenoma



Credit:Andres Martin Acosta MD @Andres_M_Acosta

NEPHROGENIC METAPLASIA (NEPHROGENIC ADENOMA)

MORPHOLOGY

- **Papillary, tubular, tubulocystic**, or flat lesions lined by **hobnail epithelial cells**
- No atypia, mitosis, necrosis, solid growth, invasion

OTHER HIGH YIELD POINTS

- Chronic irritation of urothelium with **metaplastic** change or exfoliated renal tubular cells get implanted at sites of irritation and proliferate
- Benign
- IHC: Positive: **PAX8,** PAX2, CK7, **AMACR**; Negative: PSA, p53, GATA3, p63

Path Presenter

URINARY BLADDER: NEOPLASTIC

WHO 2022 CLASSIFICATION OF BLADDER TUMORS

• UROTHELIAL TUMORS

Non-invasive urothelial neoplasms
Urothelial papilloma
Inverted urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-invasive papillary urothelial carcinoma, low-grade
Non-invasive papillary urothelial carcinoma, high-grade
Urothelial carcinoma in-situ (CIS)
Invasive urothelial neoplasms
Invasive urothelial carcinoma

URINARY BLADDER: NEOPLASTIC

WHO 2022 CLASSIFICATION OF BLADDER TUMORS

• SQUAMOUS CELL NEOPLASMS OF URINARY TRACT

Urothelial squamous papilloma
Verrucous carcinoma of the bladder
Pure urothelial squamous cell carcinoma

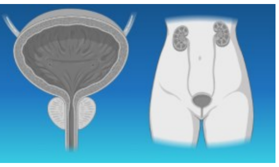
• GLANDULAR NEOPLASMS OF URINARY TRACT

Villous adenoma
Adenocarcinoma, NOS

• URACHAL AND DIVERTICULAR NEOPLASMS

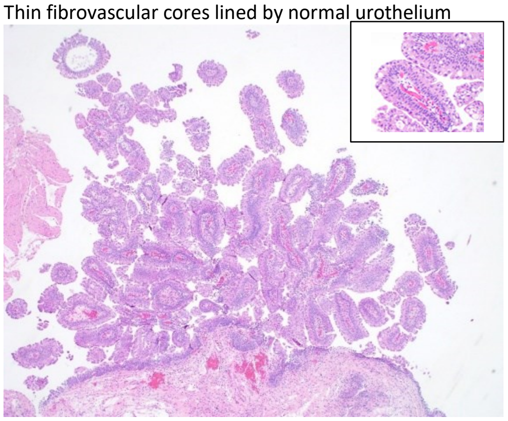
Urachal carcinoma
Diverticular carcinoma

14. UROPATHOLOGY



•TUMORS OF MULLERIAN TYPE	• URETHRAL NEOPLASMS
Clear cell adenocarcinoma of the urinary tract **Endometrioid carcinoma of the urinary tract**	Littre gland carcinoma of urethra Skene gland carcinoma of the urethra Cowper gland adenocarcinoma of the urethra

Thin fibrovascular cores lined by normal urothelium



Credit: Andres Martin Acosta MD@Andres_M_Acosta

UROTHELIAL PAPILLOMA

MORPHOLOGY

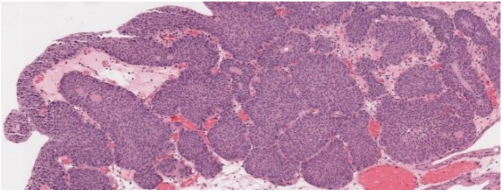
- **Solitary**, exophytic, **thin fibrovascular cores** lined by normal urothelium (4-7 layers, **normal thickness**) without cytologic atypia
- Non-branching, non-fused papillae; +/- ballooning of umbrella cells

OTHER HIGH YIELD POINTS

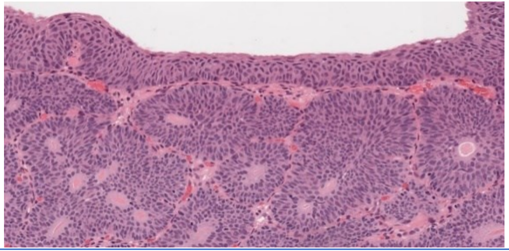
- Benign, age range: 8-87 years, majority 5th decade, M>F
- Locations: Trigone, other; Size: 2-3 cm
- Pathogenesis: **HRAS, KRAS mutations**
- Gross: Polypoid/papillary
- DD: Polypoid/papillary cystitis (broad edematous core, inflammation)
- IHC: Positive: CD44 (basal cells), Ck20 (umbrella cells) like normal urothelium

Path Presenter

Inverted/endophytic pattern, anastomosing and proliferating cords of urothelial cells



Palisaded basal cells at the periphery of cords



INVERTED UROTHELIAL PAPILLOMA

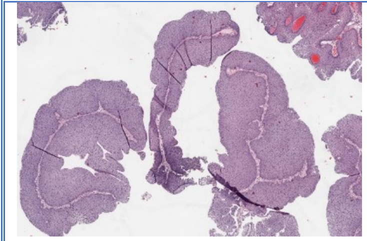
MORPHOLOGY

- **Inverted**/endophytic pattern, anastomosing and proliferating cords of urothelial cells with maintained polarity, palisaded basal cells at the periphery of cords surrounding central streaming urothelial cells, and **normal thickness**
- No atypia

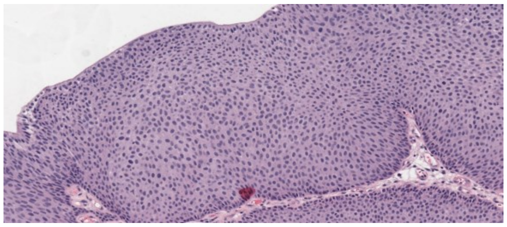
OTHER HIGH YIELD POINTS

- **Benign**, age group: any age
- Locations: Bladder neck, trigone, followed by renal pelvis, ureter, urethra; Gross: Polypoid
- Pathogenesis: **HRAS, KRAS mutations**
- Differential diagnosis: Other inverted papillary tumors like LGPUC, HGPUC, invasive urothelial ca
- IHC: Positive: CD44 (basal cells); Negative: CK20, p53

Path Presenter



Fibrovascular cores lined by thickened urothelium with mild cytologic atypia



PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL

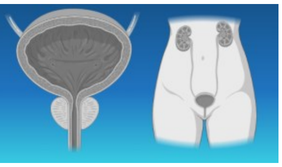
MORPHOLOGY

- Papillary architecture, **fibrovascular cores** lined by **thickened urothelium** with mild cytologic atypia (**monotonous appearing cells** with mild nuclear enlargement); **not** appreciable at low magnification
- No marked cytologic atypia (easily appreciated at low magnification)

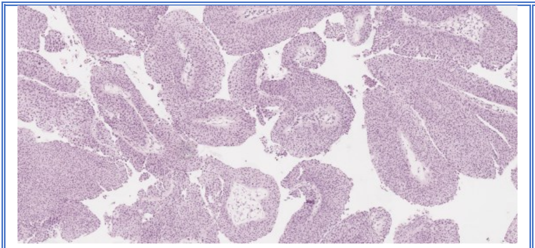
OTHER HIGH YIELD POINTS

- Age group: 6th to 7th decade, M>F, Without a history of urothelial carcinoma
- Pathogenesis: Not known, **some cases with TERT promoter and FGFR3 mutations**
- Cystoscopy: Papillary lesion, small, single
- Gross: Papillary lesion; IHC: Not useful

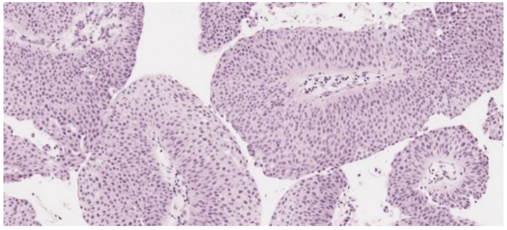
Path Presenter



14. UROPATHOLOGY



Papillary architecture, fibrovascular cores lined by urothelial cells of variable thickness with or without mild cytologic atypia



NON-INVASIVE PAPILLARY UROTHELIAL CARCINOMA, LOW-GRADE

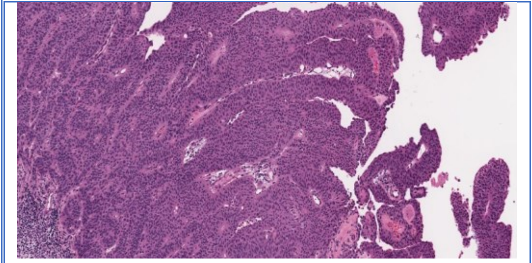
MORPHOLOGY

- **Papillary** architecture, **fibrovascular cores** lined by urothelial cells of **variably increased thickness** with or without mild cytologic atypia (**mild** nuclear enlargement, hyperchromasia, and size variation), mild loss of polarity, not appreciable at low magnification
- No marked cytologic atypia (easily appreciated at low magnification)
- Mitosis mostly basal
- Inverted variant with an inverted growth pattern

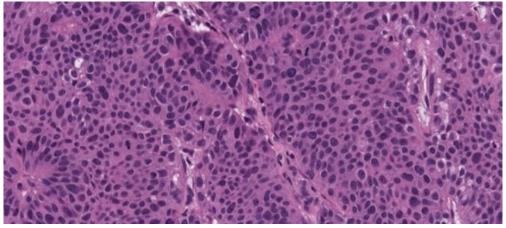
OTHER HIGH YIELD POINTS

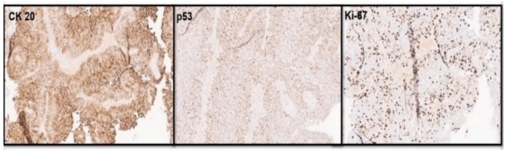
- Age group: >60 years, M>F; Risk factors: Smoking, chemical exposure
- Pathogenesis: **FGFR3 alterations, TERT promoter mutations**
- Cystoscopy/gross: Exophytic papillary tumor, single or multiple, variable size
- Prognosis: Frequent recurrence (50%), rare progression to invasive urothelial carcinoma, IHC: Not useful

Path Presenter



Fibrovascular cores lined by urothelial cells of variable thickness with marked cytologic atypia





NON-INVASIVE PAPILLARY UROTHELIAL CARCINOMA, HIGH-GRADE

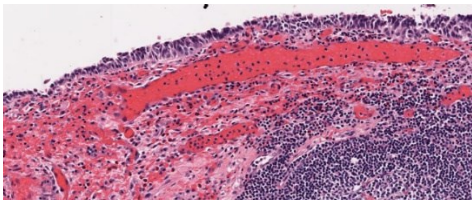
MORPHOLOGY

- **Papillary architecture**, **fibrovascular cores** lined by urothelial cells of **variably increased thickness** with **marked cytologic atypia** (marked nuclear enlargement, hyperchromasia, prominent nucleoli, irregular contours, and size variation), loss of polarity/disordered architecture, easily appreciable at low magnification
- Frequent mitosis, including atypical forms
- More complex and fused papillae compared to LGPUC
- **High grade features present in at least 5% of total tumor**
- Inverted variant with an inverted growth pattern

OTHER HIGH YIELD POINTS

- Mean age: 70 years, 3M:1F
- Risk factors: Smoking, chemical exposure
- Pathogenesis: **TERT promoter mutations, FGFR3 alterations, p53 mutations, p16 loss (chromosome 9p)**
- Cystoscopy: Exophytic papillary tumor, single or multiple, variable size, less translucent than LG
- Prognosis: **Frequent recurrence (60%), progression to invasive urothelial carcinoma (25%)**
- IHC: Positive: CK20 (full thickness), increased Ki67; Negative: CD44

Path Presenter

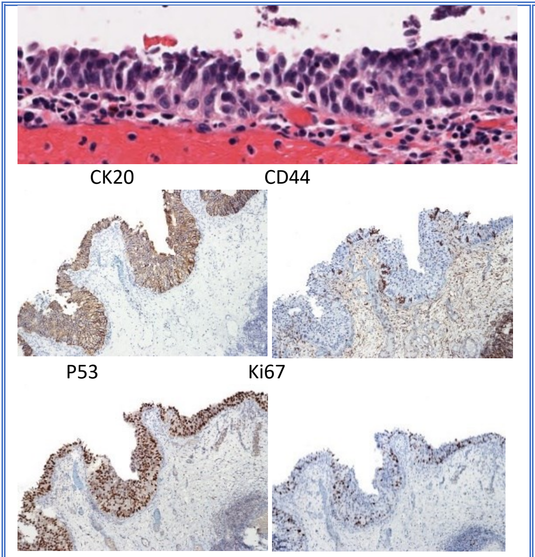


Markedly atypical urothelial cells, disordered architecture/loss of polarity

UROTHELIAL CARCINOMA IN-SITU

MORPHOLOGY

- **Flat lesion** of variable thickness, **markedly atypical urothelial cells,** disordered architecture/loss of polarity
- No papillary architecture
- Variants: Pagetoid (single cells growing in a pagetoid manner), clinging (mostly denuded with few attached malignant cells), glandular



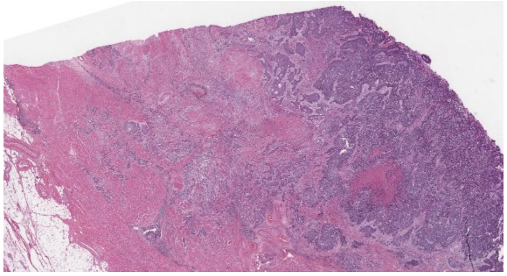
Credits: Corus13@Rus13co

OTHER HIGH YIELD POINTS

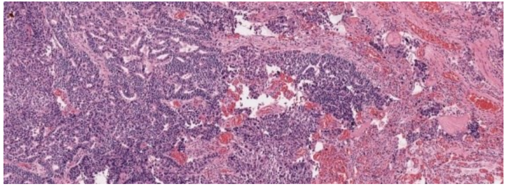
- Affects elderly patients
- Pathogenesis: **TERT promoter alterations, p53, DNA damage repair genes, PI3K and MAPK pathways**
- Cystoscopy: Erythematous mucosal patches, difficult to identify, can be multifocal
- Prognosis: **Frequent recurrence and progression to invasive urothelial carcinoma**
- Differential diagnosis: Urothelial dysplasia (cytologic atypia of a neoplastic process but falls short of a diagnosis of CIS)
- FISH: UroVision chromosomes 3,7,17, 9p21
- IHC: Not necessary in classic cases
  Positive: CK20 (full thickness), p53, increased Ki67
  Negative: CD44 (or decreased)

Path Presenter

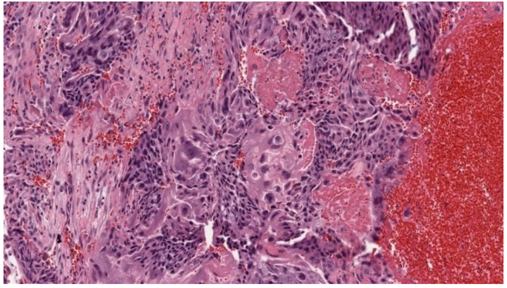
INVASIVE UROTHELIAL TUMORS



Nests, sheets, cords, or single cells invading lamina propria and beyond



Conventional invasive urothelial carcinoma with focal squamous differentiation



Plasmacytoid urothelial carcinoma
Credit: Andres Martin Acosta MD @Andres_M_Acosta

INVASIVE UROTHELIAL CARCINOMA, CONVENTIONAL TYPE

MORPHOLOGY

- Nests, sheets, cords, or single cells **invading lamina propria** and beyond
- Mixed architectural patterns

OTHER HIGH YIELD POINTS

- Seventh decade or later, **4M:1F**
- Locations: urinary bladder, 10% upper tract (renal pelvis, ureter)
- Risk factors: Smoking, radiation, chemicals-benzidine dyes, opiates, high socioeconomic status,
- Pathogenesis: **TERT promoter mutations, TP53 mutations**, others
- Gross: Sessile, ulcerated, polypoid, or papillary
- IHC: Positive: GATA3, HMWCK, CK7, CK20, P63, uroplakin**,**
  Negative: PAX8

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UROTHELIAL CA WITH DIVERGENT DIFFERENTIATION

UROTHELIAL CARCINOMA WITH SQUAMOUS DIFFERENTIATION

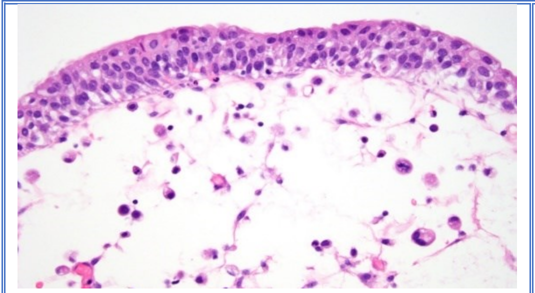
- Conventional invasive urothelial carcinoma with focal squamous differentiation (30-40% cases)

UROTHELIAL CARCINOMA WITH GLANDULAR DIFFERENTIATION

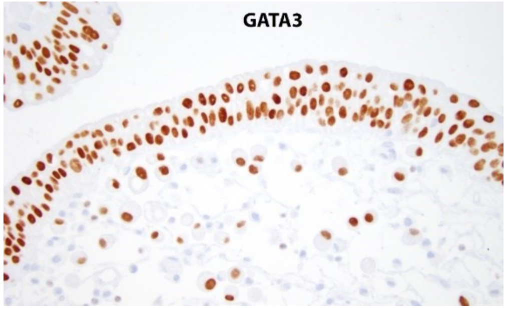
- Conventional invasive urothelial carcinoma with focal glandular differentiation (up to 18% cases)

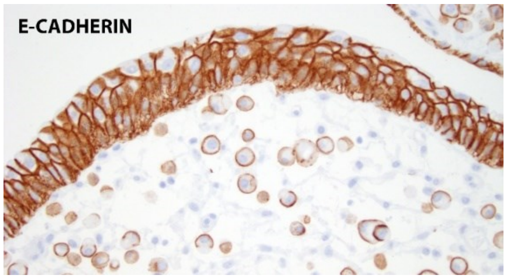
UROTHELIAL CARCINOMA WITH TROPHOBLASTIC DIFFERENTIATION

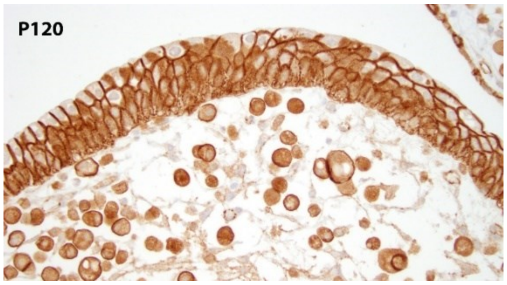
- Conventional invasive urothelial carcinoma with cytotrophoblasts and syncytiotrophoblasts
- Can resemble choriocarcinoma
- Associated with increased serum Beta HCG



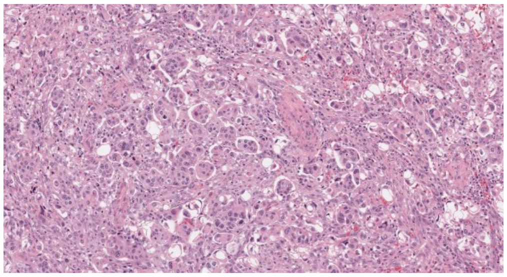
Plasmacytoid cells, singly infiltrating cells, with or without cytoplasmic lumina or vacuoles







Giant cell urothelial carcinoma



HISTOLOGIC SUBTYPES OF UROTHELIAL CA

MICROPAPILARY UC

- **Micropapillary (without fibrovascular cores) clusters of tumor cells surrounded by lacunae/clefts**
- Multiple clusters in 1 lacuna are characteristic
- **Aggressive, frequent LVI, HER2 overexpression**

NESTED UC

- Small round to ovoid nests of bland urothelial cells **resemble Von Brunn nests**
- Clues: Infiltrating nests, cytologic atypia evident on deeper nests
- **Aggressive**
- TERT promoter mutation

LARGE NESTED UC

- Medium to large nests with rounded to circumscribed borders
- Aggressive

PLASMACYTOID UC

- Plasmacytoid cells, singly infiltrating cells, with or without cytoplasmic lumina or vacuoles
- **Mutations of CDH1gene leading to loss of E-cadherin** (similar to lobular carcinoma of the breast)
- IHC: Positive for CD138, P63, GATA3, cytoplasmic P120, and negative or partial membranous E-cadherin
- **Aggressive**

Path Presenter

TUBULAR AND MICROCYSTIC UC

- **Small tubules** and **microcystic spaces** lined by cytologically bland cells
- Clues: **Infiltrating nests**

SARCOMATOID UC

- **Resemble spindle cell sarcoma** or **undifferentiated pleomorphic sarcoma** +/- heterologous differentiation
- IHC: Positive P63, GATA3, HMWCK
- **Aggressive**

LIPID RICH UC

- Typically seen admixed with conventional UC or other subtypes
- **Lipoblasts-like cells** with cytoplasmic vacuoles and nuclear indentation
- Lipid in the cytoplasm by EM and IHC

CLEAR CELL/GLYCOGEN-RICH UC

- **Glycogen containing clear cells**
- IHC: Same to conventional UC
- Should be differentiated from clear cell adenocarcinoma

LYMPHOEPITHELIOMA-LIKE UC

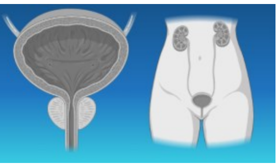
- Undifferentiated syncytial cell clusters with **dense lymphocytic, plasma cells** and other inflammatory cells infiltrate
- IHC: Negative for EBV, HPV
- Admixed with other types

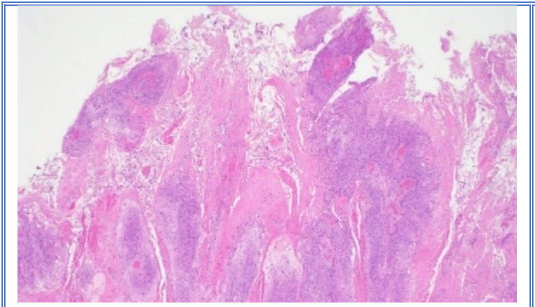
GIANT CELL UC

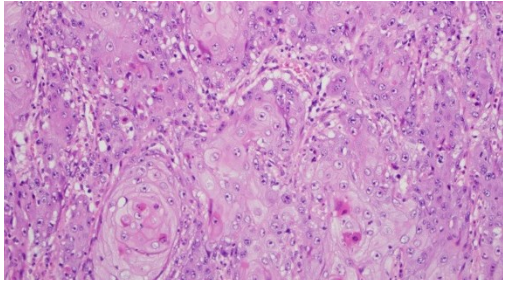
- Often with **conventional UC with pleomorphic giant tumor cells**
- Highly aggressive

POORLY DIFFERENTIATED UC

- Lacks urothelial differentiation; need IHC for confirmation of epithelial origin
- Aggressive



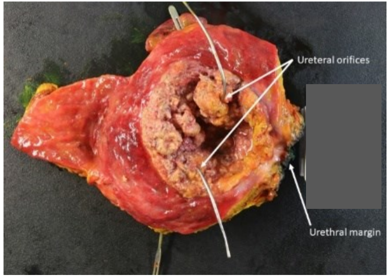

Squamous morphology with the presence of intercellular bridges, keratin pearls


Credit: Andres Martin Acosta MD @Andres_M_Acosta

PURE SQUAMOUS CELL CARCINOMA OF URINARY BLADDER

MORPHOLOGY

- **Pure (100%) squamous morphology** with the presence of intercellular bridges, keratin pearls, keratinized cells
- **Should not contain conventional UC**
- OTHER HIGH YIELD POINTS
- Indwelling catheter >10 years, bladder stones, smoking, Schistosoma haematobium infection (Egypt, Sudan)
- Pathogenesis: Chronic inflammation, loss of chromosome 17q and18p in Schistosoma associated cases
- Gross: Large tumors, solid, polypoid, nodular, or ulcerated



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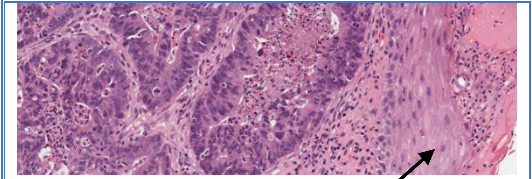
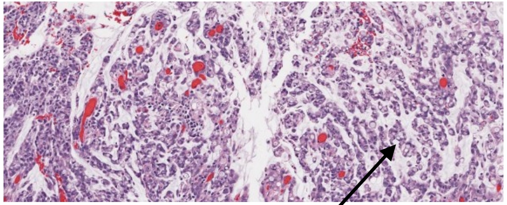
- Prognosis: Worse than conventional
- IHC: Positive: CK5, CK6, p63, desmoglein3; Negative: Uroplakins


Enteric colonic type of morphology


Signet ring type morphology

ADENOCARCINOMA, NOS OF URINARY BLADDER

MORPHOLOGY

- **Pure (100%) adenocarcinoma** morphology
- Various patterns: enteric/colonic type, mucinous, signet ring cell, or mixed; should not contain conventional UC

OTHER HIGH YIELD POINTS

- Rare, 2%, Peak age: 7th decade
- Locations: urinary bladder, renal pelvis urethra
- Pathogenesis: Unknown, chronic irritation
- Gross: Single, sessile, nodular, ulcerated
- IHC: **Positive: CK20, CDX2, Villin +/- CK7, Nuclear beta-catenin Negative: GATA3 (can be + in some cases)**

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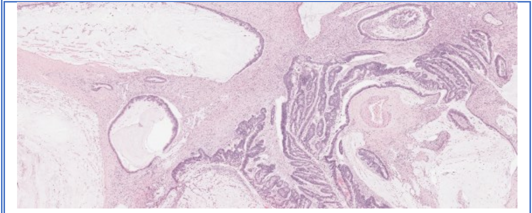
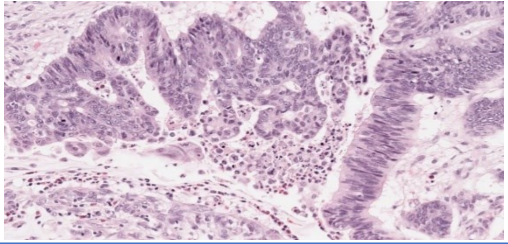

Glandular and cribriform glands and central necrosis



URACHAL CARCINOMA

MORPHOLOGY

- **Enteric adenocarcinoma morphology** with glandular and cribriform glands and central necrosis
- Sharp demarcation between carcinoma and urothelium
- Mucinous variant with pools of extracellular mucin

OTHER HIGH YIELD POINTS

- Diagnosis of exclusion
- **Arise from the urachal remnant**, rare; 6th to 7th decade 1.4 M: 1F
- Locations: Dome, anterior wall, midline from the umbilicus to bladder
- Gross: Cystic or non-cystic tumors
- Prognosis: Commonly metastasizes to the bones, lungs, liver
- IHC: Positive: CK20, CDX2; Negative: GATA3

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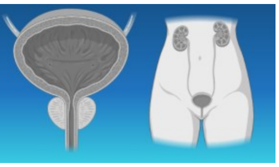


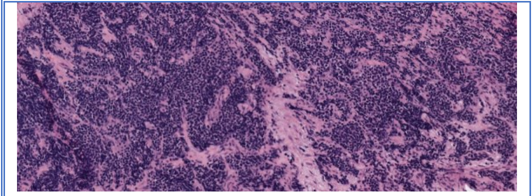
CLEAR CELL ADENOCARCINOMA

MORPHOLOGY

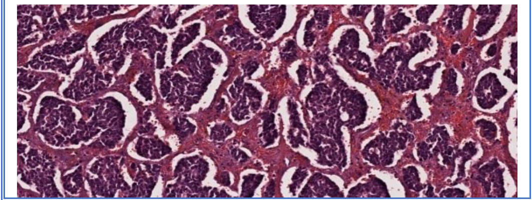
- Mixed pattern, solid, papillary, tubulocystic, lined by **hobnail cells with clear to eosinophilic cytoplasm**

OTHER HIGH YIELD POINTS

- **Thought to be Mullerian origin**, rare, 4.6 F:1M
- Locations: **Urethra (most common),** urinary bladder
- Pathogenesis: Unknown
- Gross: Solitary, polypoid, or ulcerative
- IHC: Positive: PAX8; Negative: GATA3



Solid or nested architecture



SMALL CELL NEUROENDOCRINE CARCINOMA OF BLADDER

MORPHOLOGY

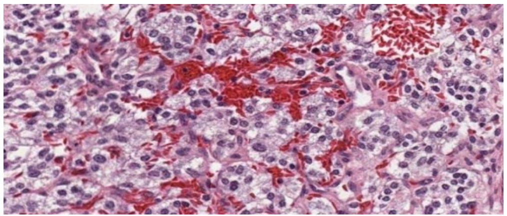
- **Morphology similar to lung** or other tumors with the presence of small cells, high nuclear-cytoplasmic ratio, crush artifact, necrosis, apoptosis

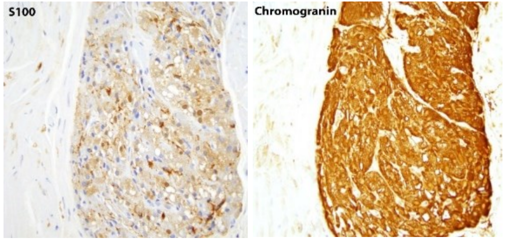
OTHER HIGH YIELD POINTS

- 5th to 8th decade, M>F
- Pathogenesis: **Inactivation of RB1 gene**
- **Aggressive, poor prognosis**
- IHC: Positive: **synaptophysin, chromogranin, INSM1, TTF1+/-**

Path Presenter

Zell-ballen architecture





Credit: Andres Martin Acosta @Andres_M_Acosta

PARAGANGLIOMA INVOLVING BLADDER

MORPHOLOGY

- Morphology is similar to paraganglioma elsewhere
- **Nested architecture (zell-ballen), separated by fibrovascular network and sustentacular cells**, cytoplasm granular or clear or amphophilic
- Scattered atypical cells

OTHER HIGH YIELD POINTS

- 5th to 6th decade, F>M, rare
- Pathogenesis: **subset with SDH mutation**
- **It can be mistaken for invasive urothelial carcinoma**
- Good prognosis
- IHC: Positive: synaptophysin, chromogranin, S100 (sustentacular cells), GATA3; Negative: CK, SDH

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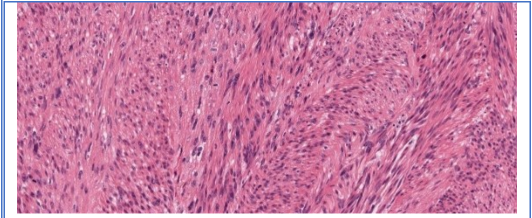
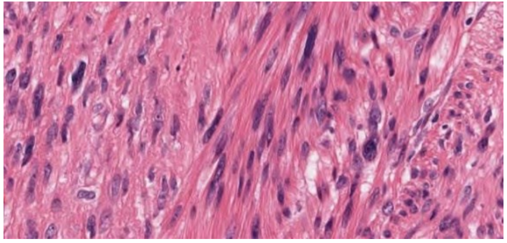


Marked cytologic atypia, nuclear hyperchromasia



LEIOMYOSARCOMA OF BLADDER

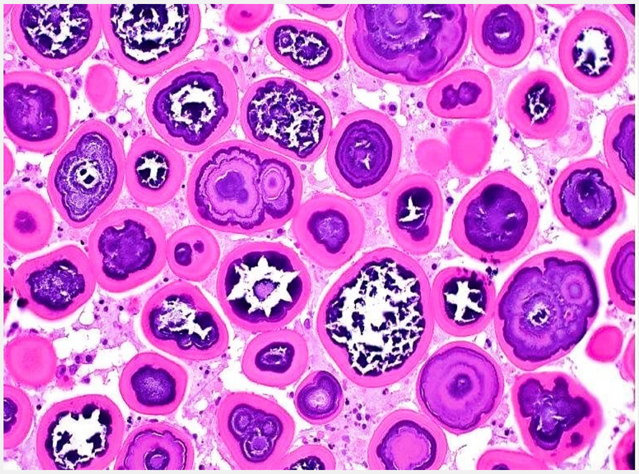
MORPHOLOGY

- Morphology is similar to soft tissue leiomyosarcoma
- **Spindle cell proliferation, perpendicular fascicles,** bright eosinophilic cytoplasm, marked cytologic atypia, nuclear hyperchromasia, mitosis, necrosis, increased cellularity
- +/- epithelioid or pleomorphic cells

OTHER HIGH YIELD POINTS

- Peak 7th decade, F>M
- **Aggressive**
- IHC: Positive: **SMA, MSA, h-Caldesmon, desmin**
  Negative: CK, EMA, CD34, S100, HMB45, myogenin, MyoD1

Path Presenter



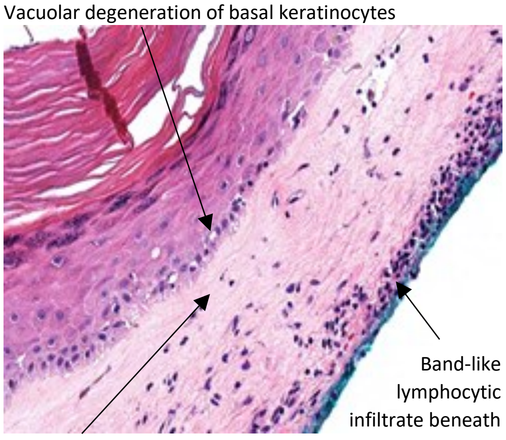
Psammoma bodies in high grade Serous carcinoma of ovary (H&E stain). Image courtesy: Rachael van der Griend, MD

CHAPTER 15: GYNECOLOGIC PATHOLOGY

Swati Bhardwaj, MD
Sudarshana Roy Chowdhury, MD
Nupur Sharma, MD
Snehal Sonawane, MD
Kenechukwu Ojukwu, MD
Terrance Lynn, MD
Jared T. Ahrendsen, MD, PhD

For Ovary and Fallopian tube: some images are courtesy of Department of Pathology, Mount Sinai Hospital

VULVA


Vacuolar degeneration of basal keratinocytes
Band-like lymphocytic infiltrate beneath collagen
Dermal sclerosis

LICHEN SCLEROSUS (LICHEN SCLEROSUS ET ATROPHICUS)

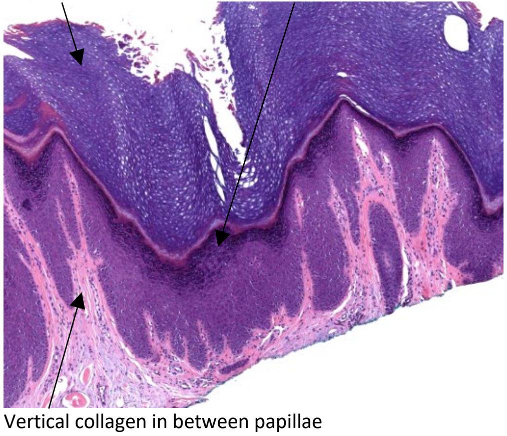
MORPHOLOGY

- **Sclerosis/hyalinization with edema of the papillary dermis** with or without erythrocyte extravasation
- May have **vacuolar degeneration** of basal keratinocytes
- **Band-like lymphocytic infiltrate** beneath homogenized collagen
- Overlying **epidermal atrophy** with rete effacement

OTHER HIGH YIELD POINTS

- **Autoimmune** disease, most common in **post-menopausal women**
- Clinically appears as white to red plaques with wrinkling and hypopigmentation resembling **"tissue paper"**
- Causes pruritis and pain, **increases the risk of differentiated VIN**

Path Presenter


Hyperkeratosis
Hypergranulosis
Vertical collagen in between papillae

LICHEN SIMPLEX CHRONICUS

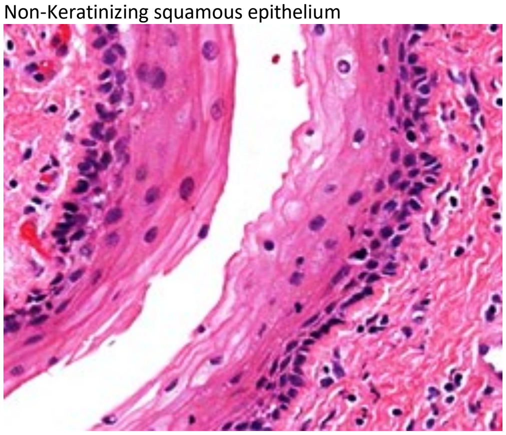
MORPHOLOGY

- **Marked hyperkeratosis** (sometimes parakeratosis)
- Hypergranulosis, **irregular psoriasiform-epidermal hyperplasia**
- Thickened papillary dermis, vertical collagen between papillae
- May have pigment incontinence or neural hyperplasia/hypertrophy
- Lots of spongiosis? → consider contact dermatitis
- Neutrophils in stratum corneum? → consider fungal → PAS/GMS

OTHER HIGH YIELD POINTS

- Non-specific pattern in response to **chronic rubbing/scratching**
- Can be also seen with infection (e.g., Candida), contact dermatitis
- Clinically looks thickened, leathery, and scaled ("lichenification")

Path Presenter


Non-Keratinizing squamous epithelium

BARTHOLIN'S DUCT CYST

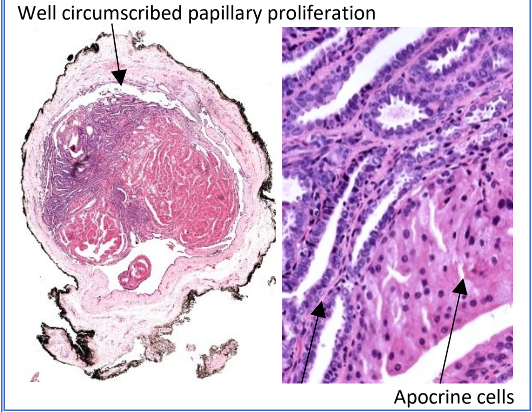
MORPHOLOGY

- **Unilocular** with a **smooth inner lining** of non-keratinizing squamous, transitional, or mucinous epithelium
- Can have foci of squamous metaplasia or have epithelial denudement

OTHER HIGH YIELD POINTS

- Vulvar cyst due to Bartholin gland duct **outlet obstruction** with subsequent retention of mucinous secretions (duct enlarged into a cyst)
- Located in the posterior vestibule
- Differential diagnosis:
    - ➢ Gartner duct cyst – mesonephric origin, usually located in the anterolateral vaginal wall at 11 o'clock and 1 o'clock regions, lined by a single layer of cuboidal to low columnar epithelium

Path Presenter



HIDRADENOMA PAPILLIFERUM

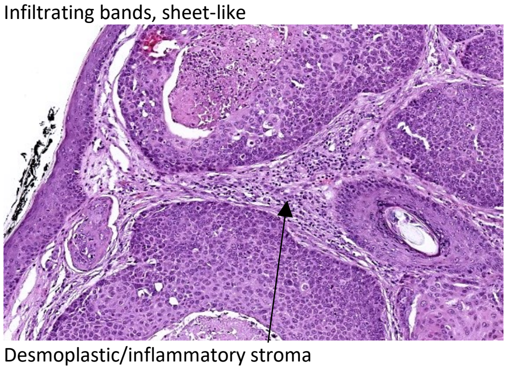
MORPHOLOGY

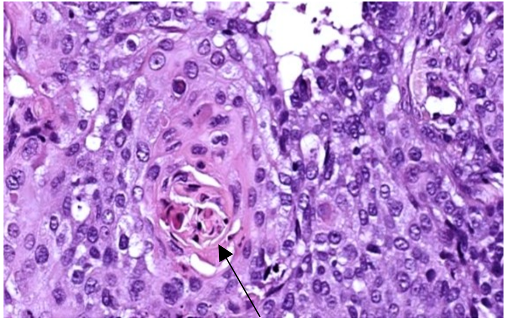
- Dermal based lesion with **maze like papillary proliferation** with tubular glands
- **Apocrine differentiation** with apical snouts
- **Two cell layers** (inner epithelial & outer myoepithelial) are seen on IHC
- May have high mitotic rate but does not always indicate malignancy

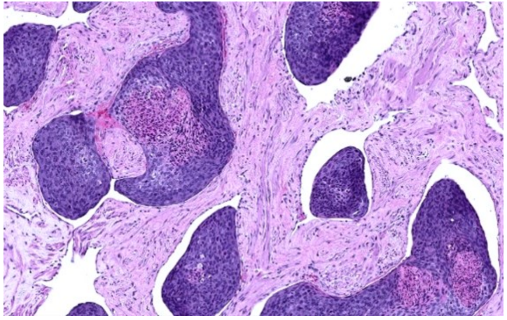
OTHER HIGH YIELD POINTS

- **Benign**, often presents as an asymptomatic **nodule**
- Virtually identical to intraductal papilloma of the breast
- **Well-circumscribed** subepithelial nodule and often small (<1 cm)

Path Presenter


Infiltrating bands, sheet-like
Desmoplastic/inflammatory stroma


Keratinizing SCC: squamous pearl


Basaloid squamous cell carcinoma

SQUAMOUS CELL CARCINOMA

MORPHOLOGY

- **Invasive** epithelial tumor composed of squamous cells with varying degrees of differentiation
- Sheet-like growth with infiltrating bands and single cells
- Often **desmoplastic/inflammatory stroma**

OTHER HIGH YIELD POINTS

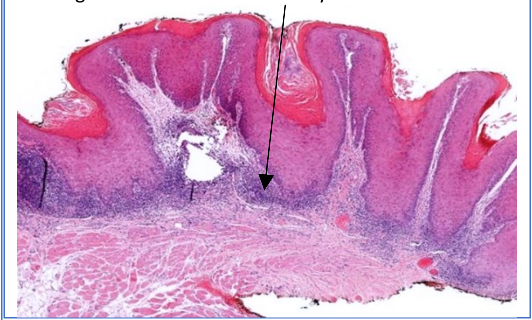
- Derived from **HSIL (HPV-related)** or **differentiated VIN (not HPV-related)**
- **Most common vulvar malignancy**, most common in elderly
- Most important factor determining the outcome: **lymph node status**
- Most important factor determining LN metastases: **depth of invasion**
- Femoral and inguinal lymph nodes are the sites of regional spread

MAIN MORPHOLOGICAL TYPES OF SQUAMOUS CELL CARCINOMA

	Keratinizing squamous cell carcinoma	Basaloid squamous cell carcinoma
High-risk HPV association	No	Yes (type 16 >18)
Precursor lesion	Differentiated VIN	Classic (usual) VIN
Associated inflammatory lesion	Lichen sclerosus	N/A
Morphology	Keratinizing	Warty, basaloid
Age	Older	Younger
IHC	p16 negative p53 positive (some cases)	p16 diffuse positive p53 negative

Link Link

Pushing invasion with inflammatory infiltrate



VERRUCOUS CARCINOMA

MORPHOLOGY

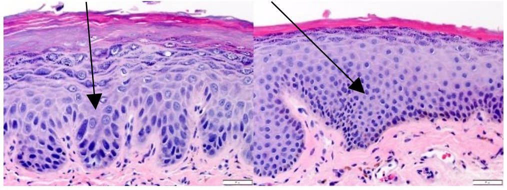
- **Highly differentiated**, **exophytic** SCC variant with prominent acanthosis
- Minimal nuclear atypia, superficial cells with abundant eosinophilic cytoplasm, and **broad "pushing" invasion** (non-infiltrative) with an associated inflammatory infiltrate

OTHER HIGH YIELD POINTS

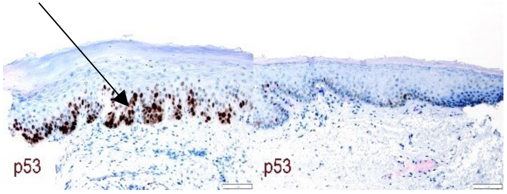
- Lymph node metastases are very rare

Path Presenter

Differentiated VIN Normal Squamous epithelium



P53 staining all basal cells in VIN



Courtesy: @DermpathL

DIFFERENTIATED-TYPE VULVAR INTRAEPITHELIAL NEOPLASIA

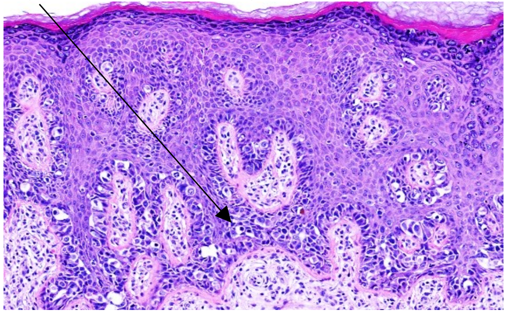
MORPHOLOGY

- **Basal cell atypia with nuclear hyperchromasia**, anastomosing of rete ridges, atypical basal mitoses, prominent nucleoli
- **Superficial terminal differentiation** (cornification) with hyperkeratosis and dyskeratosis

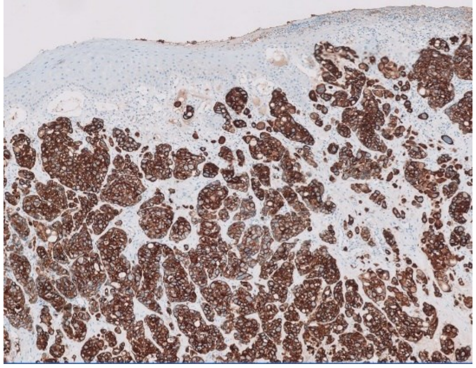
OTHER HIGH YIELD POINTS

- **HPV-negative** squamous dysplasia
- Predominantly in **elderly women**, associated with lichen planus and lichen sclerosus
- Higher risk/quicker progression to invasive SCC than normal VIN3, so treat with excision
- IHC: p16 negative (non-block positive), **p53 mutant** with strong staining of all basal cells, Ki67 profoundly increased

Paget cells, single cells or in groups/glands



CK7 postive cells



EXTRAMAMMARY PAGET DISEASE

MORPHOLOGY

- **Large, round "Paget" cells** with prominent pale cytoplasm and nucleoli **spreading throughout the epithelium**
- Can be single cells or in groups/glands
- Can extend down adnexal structures
- Important to rule out cutaneous pagetoid spread of urothelial, melanoma, or GI cancer with IHC (see below)

OTHER HIGH YIELD POINTS

- Often elderly Caucasian women with red, pruritic lesion

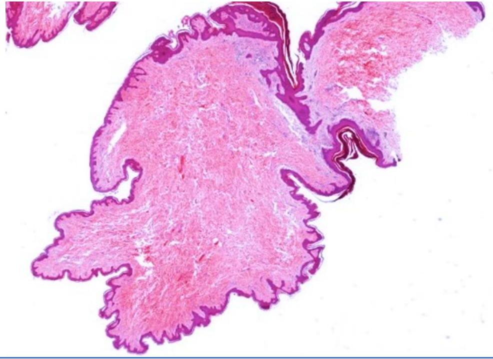
	CK7	CK20	GCDFP-15	CDX-2	CEA	S100	UPK III	HER2	GATA-3
PPD	+	-	+	-	+	-	-	+	+
UC	+	+	-	-	-	-	+	-	+
ARC	+/-	+	-	+	+	-	-	-	-
M	-	-	-	-	-	+	-	-	-

PPD: Primary Paget's disease; UC: Urothelial carcinoma; ARC: Anorectal carcinoma; M: Melanoma

Path Presenter

UNIQUE VULVAR MESENCHYMAL LESIONS

Polypoid, fibrovascular core, squamous epithelium



FIBROEPITHELIAL STROMAL POLYP

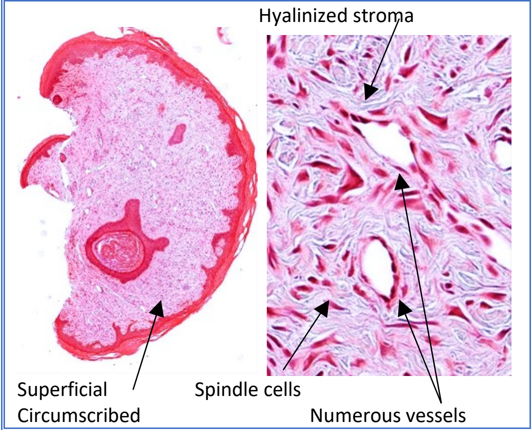
MORPHOLOGY

- **Polypoid** growth with variably cellular central **fibrovascular core covered in squamous epithelium**
- The stroma contains predominantly bland spindled cells
- Can see multinucleated stroma cells with degenerative-type atypia, including significant pleomorphism

OTHER HIGH YIELD POINTS

- **Benign**, in reproductive age women, can grow during pregnancy

Path Presenter



CELLULAR ANGIOFIBROMA

MORPHOLOGY

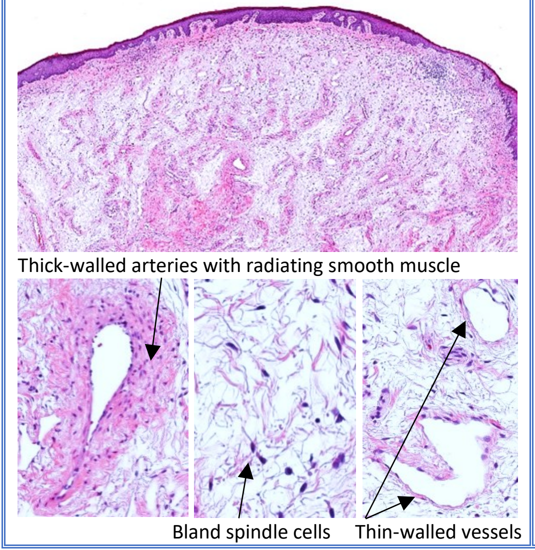
- Composed of **uniform, bland spindled cells** in a **fibrous stroma**
- Small to medium-sized blood vessels with **thick hyalinized walls**
- Sort of resembles a spindle-cell lipoma, but with **wispy collagen**

OTHER HIGH YIELD POINTS

- Rare, benign, small (<5 cm), usually painless superficial mass or polyp, circumscribed but unencapsulated, often traps fat at edges
- Most commonly **seen in pregnancy** and can **regress post-partum**
- IHC: (+) ER/PR positive, (+/-) CD34, Desmin, RB1 loss of expression

Path Presenter

Poorly circumscribed, hypocellular, infiltrative



AGGRESSIVE ANGIOMYXOMA

MORPHOLOGY

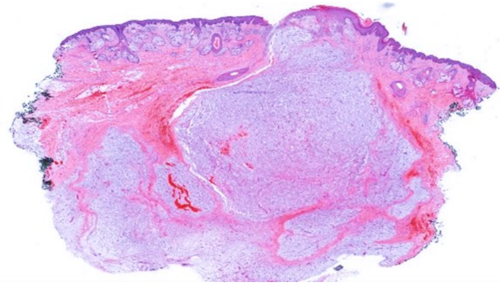
- Low-grade, hypocellular, no mitotic activity or atypia
- Composed of **small, bland spindled cells** with scant cytoplasm
- Numerous blood vessels of varying sizes, including thin-walled capillary-like and **thick-walled arteries with radiating perivascular smooth muscle**, invading fat, and muscle

OTHER HIGH YIELD POINTS

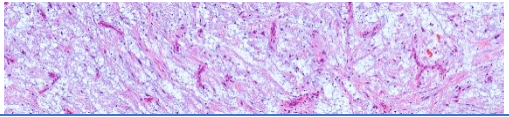
- **Benign**, but with a tendency to **recur after incomplete recurrence**
- Often presents as a "cyst" in reproductive age women
- Large (>5 cm), **poorly circumscribed, infiltrative**
- Gelatinous consistency
- IHC: (+) ER, PR, desmin, (+/-) CD34, HMGA2 positive (68%–90%), RB1 retained
- Molecular: ***HMGA2* rearrangements** (30% with *HMGA2-YAP1* fusion)
- Treatment: complete surgical resection

Path Presenter

Superficially located, multilobulated



Bland stellate and spindled cells, delicate vessels



SUPERFICIAL ANGIOMYXOMA

MORPHOLOGY

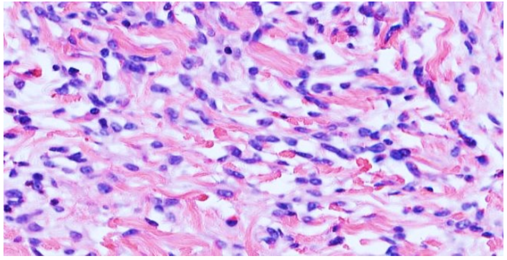
- **Bland stellate and spindled cells** and inflammatory cells (classically neutrophils), and numerous delicate **curvilinear vessels**
- Can envelope skin adnexal structures/epithelium
- **Multilobulated**, hypocellular myxoid nodules in dermis
- Well-demarcated but unencapsulated

OTHER HIGH YIELD POINTS

- Small (< 5 cm) exophytic polypoid mass in **centered in skin and subcutaneous tissue**
- Benign with localized recurrences
- IHC: (+) CD34 and vimentin, (-) ER, PR, HMGA2

Path Presenter

Oval/spindled cells in a collagenous stroma



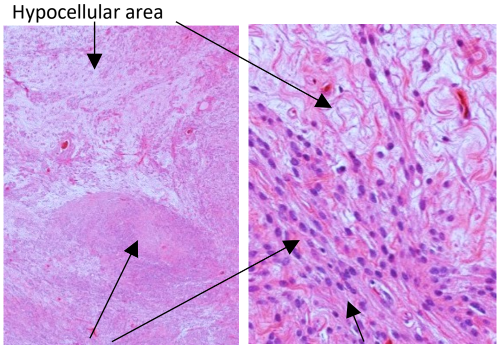
SUPERFICIAL MYOFIBROBLASTOMA

MORPHOLOGY

- Oval to spindled cells with **wavy nuclei** and scant cytoplasm
- **Fine collagenous stroma**
- **Dilated thin-walled vessels,** may give **'stag horn'** appearance

OTHER HIGH YIELD POINTS

- Benign
- Discrete, unencapsulated, usually small (< 5 cm)
- IHC: (+) Desmin, ER/PR; (+/-) CD34



Hypocellular area

Hypercellular area

Plump spindle cells

ANGIOMYOFIBROBLASTOMA

MORPHOLOGY

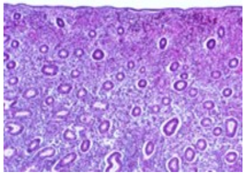
- **Alternating hypocellular and hypercellular areas**
- Spindle and plump epithelioid or plasmacytoid cells

OTHER HIGH YIELD POINTS

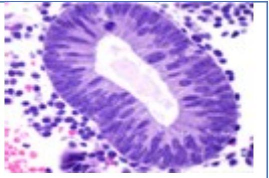
- Benign, non-recurring
- Small (<5 cm), circumscribed
- IHC: (+) Desmin, ER/PR; (+/-) CD34
- Molecular: *MTG1-CYP2E1* fusion

Path Presenter

ENDOMETRIUM



Abundant stroma

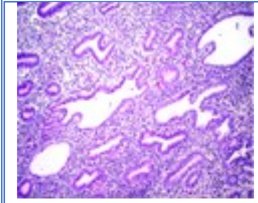


Columnar nuclei,

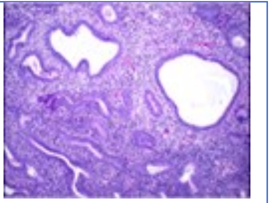
PROLIFERATIVE ENDOMETRIUM

MORPHOLOGY

- Straight or mildly tortuous **tubular glands**
- **Abundant stroma** (stroma ≥ glands)
- Columnar cells with pseudostratification
- Hyperchromatic cigar-like nuclei and mitoses



Branching glands



Cystically dilated glands

DISORDERED PROLIFERATIVE ENDOMETRIUM

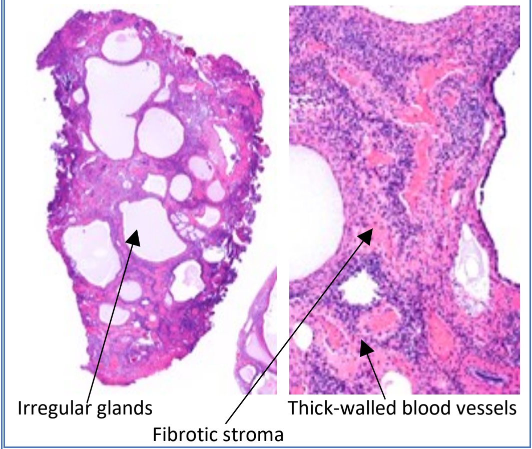
MORPHOLOGY

- **Variably shaped glands** with branching, cystically dilated
- Abundant stroma (Gland to stroma ratio <2:1)
- Cells identical to proliferative endometrium

OTHER HIGH YIELD POINTS

Often due to anovulatory cycles

15. GYNECOLOGIC PATHOLOGY



BENIGN ENDOMETRIAL POLYP

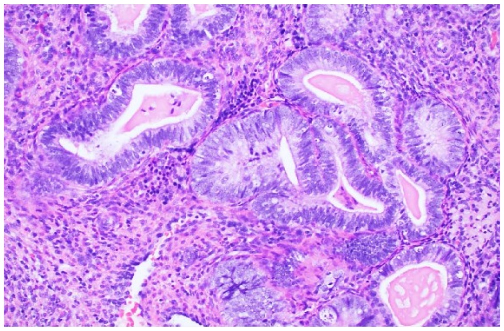
MORPHOLOGY

- Localized, disorganized altered glands & stroma with surface epithelial lining
- Glands: tubules may be simple, branched, or **cystically dilated** and lined by **inactive endometrium**
- Stroma: often **collagen-rich** containing **characteristic thick blood vessels**

OTHER HIGH YIELD POINTS

- Solitary, can be anywhere in the uterus
- Epithelial lining may have metaplasia, hyperplasia, or carcinoma; particularly **serous intraepithelial endometrial carcinoma (SIEC)** in post-menopausal patients

Path Presenter


Crowded glands; cells without atypia

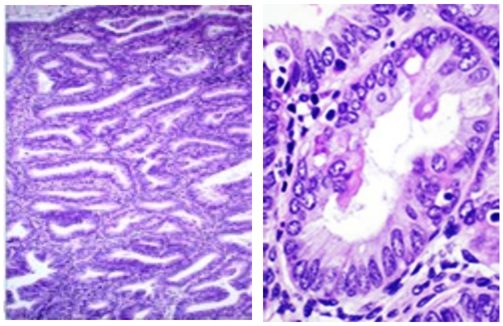
HYPERPLASIA (WITHOUT ATYPIA)

MORPHOLOGY

- **Gland crowding** (gland to stroma ratio >2:1)
- Tubular, branching, or cystically dilated glands
- Glands lined by columnar cells with cigar-shaped polarized nuclei, pseudo -stratification +/- increased mitosis (**normal nuclei/cytology**)
- Can be **simple**: tubular glands—lower risk; or **complex**: architecturally abnormal, irregular glands, with even less stroma— higher risk

OTHER HIGH YIELD POINTS

- Perimenopausal women with non-cyclical vaginal bleeding, prolonged estrogen exposure by progesterone, obesity, PCOS


Crowded glands
Cytologic atypia

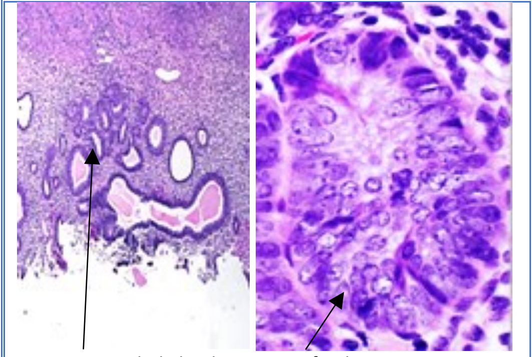
HYPERPLASIA WITH ATYPIA / COMPLEX ATYPICAL HYPERPLASIA (CAH)

MORPHOLOGY

- **Gland crowding** (gland to stroma ratio >2:1)
- Glands with **complex architecture** (branching, back-to-back)
- **Cytologically atypical nuclei**: enlarged, rounded, loss of polarity, vesicular chromatin, prominent nucleoli

OTHER HIGH YIELD POINTS

- Important to compare nuclei to non-hyperplastic glands elsewhere in the specimen to account for fixation artifact
- If nuclear atypia is too much, consider endometrioid carcinoma


> 1 mm crowded glands
Loss of polarity, atypia

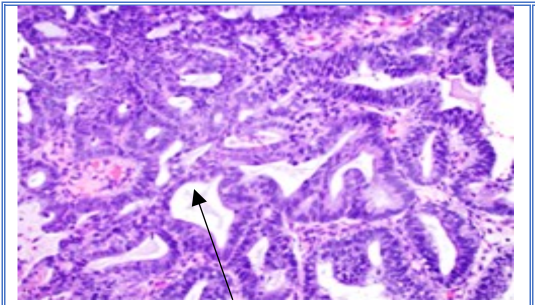
ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (EIN)

MORPHOLOGY

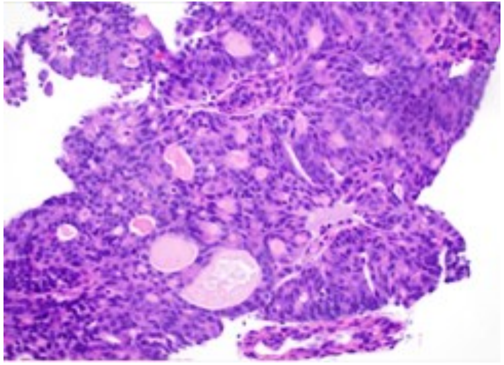
- Diagnostic criteria:
  - ➢ **Crowded glands** with a gland to stroma ratio > 1
  - ➢ **Altered cytology of the crowded glands** from background epithelium ("cytologic demarcation")
  - ➢ **Must be > 1 mm within a single tissue fragment**

OTHER HIGH YIELD POINTS

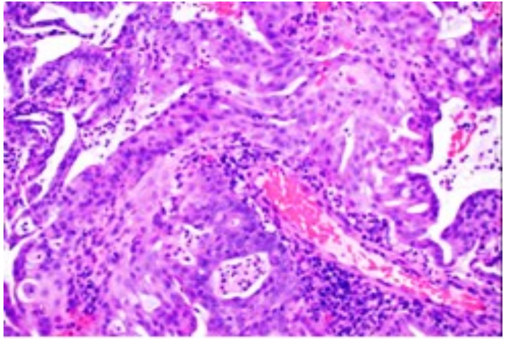
- **Same genetic changes as seen in endometrioid carcinoma** (microsatellite instability, *PAX-2* inactivation, *PTEN* inactivation, *CTNNB1* mutation)
- Although **CAH and EIN are often overlapping diagnoses**, they have slightly different diagnostic criteria; **EIN is more specific and CAH more sensitive**
- WHO accepts both; usage depends on the local practice



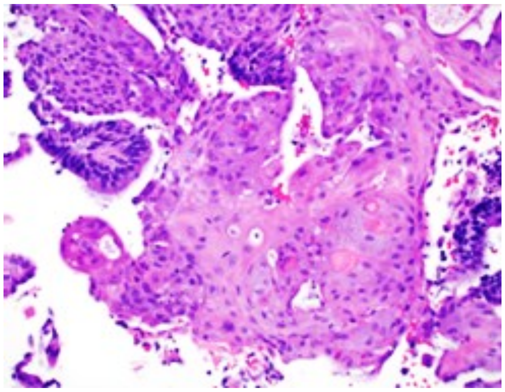
Crowded glands, smooth luminal outline



Microacinar/cribriform pattern



Squamous metaplasia



Keratin pearls

ENDOMETRIAL CARCINOMA

MORPHOLOGY

- **Crowded, complex glands** with a smooth luminal outline
- Columnar cells with eosinophilic granular cytoplasm
- Nuclear atypia usually mild to moderate
- **Distinction from CAH/EIN is based on stromal invasion**, which is defined by one of the following:
  - **Loss of intervening stroma** with a confluent/cribriform growth pattern
  - **Irregular infiltration** of the myometrium by glands associated with an altered fibroblastic stroma (desmoplastic response)
  - **Solid, non-squamous epithelial growth**
- **Complex architecture** (papillary/villoglandular)
- **Squamous differentiation** present in 10-25% of cases with **morules**, keratin pearls, and intercellular bridges
- **Corded and hyalinized**: cords, clusters, and/or trabeculae of epithelioid to spindled cells embedded within hyalinized to myxoid matrix
  - Often associated with grade 1-2 glandular component
  - It may be associated with *CTNNB1* mutation
  - No prognostic significance, but sometimes confused with carcinosarcoma, leading to overtreatment

OTHER HIGH YIELD POINTS

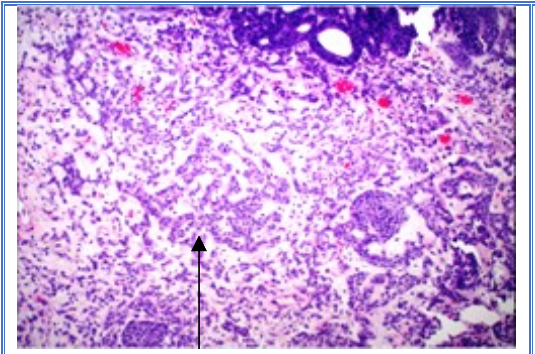
- **Most common** carcinoma of the endometrium
- Occurs in **post-menopausal women** and related to increased levels of **estrogen exposure** (associated with obesity, diabetes, PCOS, medications)
- Preceded by hyperplasia, presents with **vaginal bleeding**
- IHC: (+) CK7, PAX8, vimentin (cup-like pattern); (-) CK20
  - Low-grade often (+) ER/PR
- **FIGO grade based on the % solid, non-glandular, non-squamous growth:**
  - Grade 1: ≤5%, grade 2: 6-50%, grade 3: >50%
  - Exclude squamous morules from % of solid grade calculation
  - The grade can be increased by 1 based on severe nuclear atypia in the majority (>50%) of cells
  - A confluent microacinar pattern is often counted as solid
- Molecular classification (4 groups):

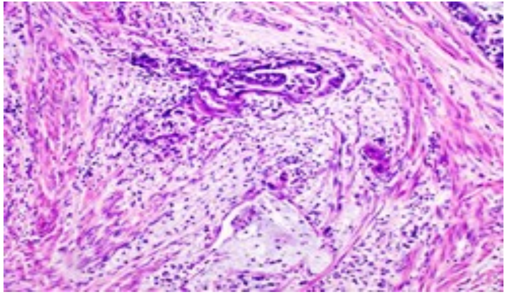
  1) Ultramutated (POLE mutated) subtype (~5%)
  - Mutations of DNA polymerase ε result in an extremely high tumor mutation rate → increased neoantigens in tumor cells → increased tumor-infiltrating lymphocytes (TILs) → **excellent prognosis**
  - Often grade 3 with intratumoral heterogeneity and giant tumor cells
  - Young patients, broad invasive front with low clinical stage

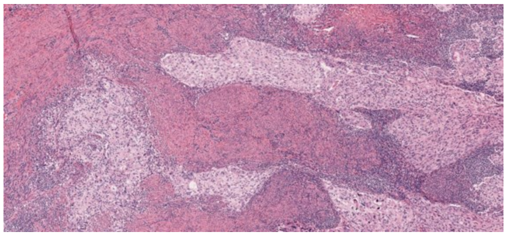
  2) Hypermutated/Microsatellite Instability (MSI) subtype (~25%)
  - Mutations in MMR proteins → high mutation rate → lots of neoantigens in tumor cells→ increased TILs; intermediate prognosis
  - Often Grade 3, substantial LVI, MELF-pattern of invasion
  - Associated with Lynch Syndrome

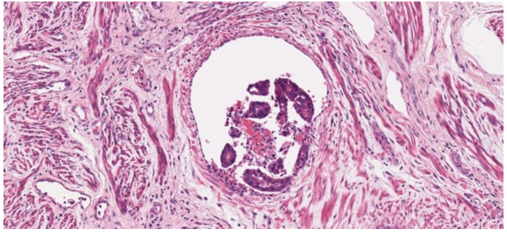
  3) Copy Number High/Serous-like subtype (~25%)
  - Genomically unstable → high somatic copy number alterations
  - Very high rate of *TP53* mutations
  - Often Grade 3 with high nuclear grade and destructive invasion
  - Often older patients and advanced stage, poor prognosis

  4) Copy Number Low/Microsatellite Stable (MSS) subtype (~45%)
  - **Most common type**, often grade 1-2, ER/PR+
  - Associated with unopposed estrogen exposure (e.g., obesity)
  - Overall low mutation rate, frequent *PTEN* mutations


Hyalinized and corded variant


MELF invasion


Myoinvasion with prominent desmoplastic response


Tumor cells within vascular space

    - ➢ Intermediate prognosis (depends largely on stage)
- Mutations in *PTEN, PIK3CA, ARID1A, CTNNB1, KRAS* often seen in all groups

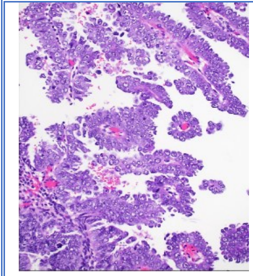
MYOINVASION

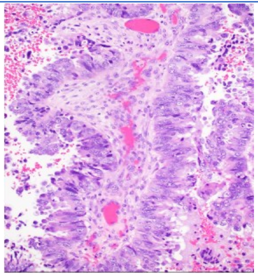
- Measure from **endomyometrial junction to deepest point of invasion**
    - ➢ Report as percentage (depth of invasion/total myometrial thickness)
- **Critical clinical cutoff point = 50%**
- Will often see **irregular angular glands** eliciting a **desmoplastic response** or **loose granulation tissue** with inflamed edematous fibrous stroma
- It can be helpful to look for compressed non-neoplastic glands to determine the level of the endomyometrial junction
- Carcinoma involving adenomyosis or within vessels does not count as invasion
- **Challenging patterns of myometrial invasion:**
    - **1) "Pushing" Invasion:**
        - ➢ Broad, expansile front with mild or absent stromal reaction
        - ➢ Submit adjacent normal endometrium if present to determine the level of endomyometrial junction
    - **2) "Microcystic, Elongated, and Fragmented" (MELF):**
        - ➢ Invasive glands lined by a single, flattened layer of epithelium with eosinophilic, squamoid cytoplasm
        - ➢ Simulate vascular spaces; associated edematous, inflamed stroma
        - ➢ More aggressive, associated with LVI and lymph node metastasis
    - **3) Diffusely infiltrative pattern:**
        - ➢ Individual well-formed glands with mild to moderate atypia that diffusely infiltrate the myometrium with minimal stromal reaction
        - ➢ Often widespread throughout the uterus

LYMPHOVASCULAR INVASION

- Frequently seen with the MELF pattern, sometimes intravascular cells can appear "histiocytoid," requiring stains to confirm that they are tumor
- **True lymphovascular invasion:**
    - ➢ The tumor cluster takes the shape of the vessel
    - ➢ Is associated with a fibrin thrombus, attached to the vessel wall
- **Extensive LVI (≥5 vessels) has prognostic significance**
- Syndromes associated with endometrioid carcinoma:
    - ➢ **Lynch Syndrome:** 50% lifetime risk (similar to the risk of colon cancer)
    - ➢ ***PTEN*-hamartoma tumor syndrome/Cowden syndrome**

Link Link Link


Complex papillae


Nuclear stratification

SEROUS CARCINOMA

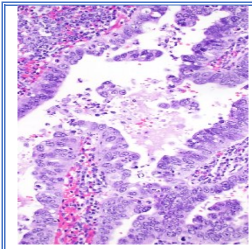
MORPHOLOGY

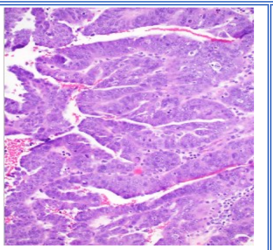
- Epithelial cells with **large, atypical nuclei, prominent nucleoli, scant cytoplasm, numerous mitoses**
- Often **complex papillary architecture**, but can also be solid or glandular
- Luminal surfaces often appear **scalloped** (no common apical border as is seen in endometrioid)

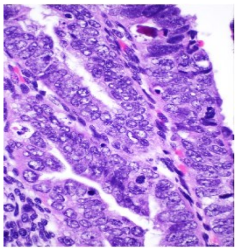
OTHER HIGH YIELD POINTS

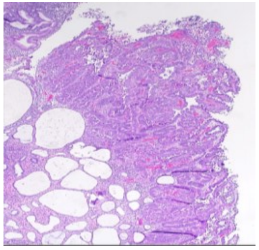
- Typically, in **post-menopausal women presenting with bleeding**
- Often grossly inconspicuous on the **surface of a polyp**
- Background endometrium is often atrophic

15. GYNECOLOGIC PATHOLOGY


Tufting/budding in gland lumen


Slit like luminal space

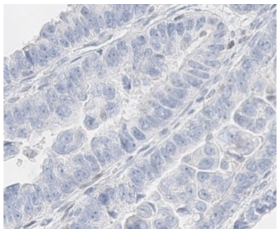

High nuclear grade


SEIC in polyp

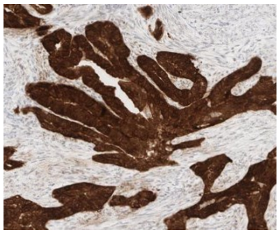
- **Serous Endometrial Intraepithelial Carcinoma (SEIC)**: precursor to serous carcinoma; confined to the epithelium (e.g., the surface of a polyp), can undergo transtubal metastasis to the pelvis
- Molecular: *TP53, PPP2R1A, PIK3CA,* and *HER2* mutations
- IHC: **p53 mutant** (aberrant diffuse overexpression, absent or null expression or cytoplasmic expression), **p16 block positive**
- **HER2/neu (*ERBB2*) expression** is identified in >30% of endometrial serous carcinoma; advanced/recurrent serous carcinoma with HER2/neu overexpression → benefit from trastuzumab
- Prognosis depends on stage (advanced = very bad); grading not applicable

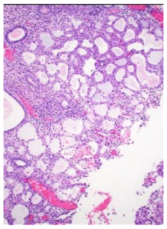
Path Presenter

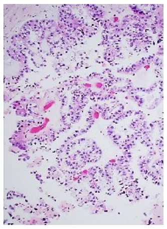
p53 (null pattern)

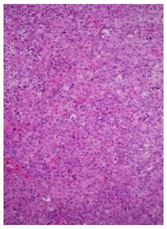


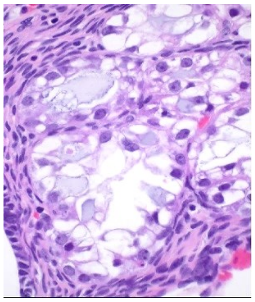
p16 (block positive)

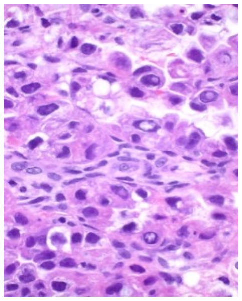



Tubulocystic


Papillary


Solid

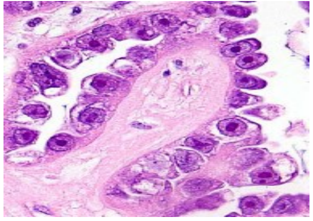

Clear cells


Oxyphilic cells

CLEAR CELL CARCINOMA

MORPHOLOGY

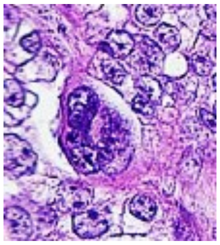
- **Polygonal/cuboidal or hobnail-shaped cells** with **clear or eosinophilic cytoplasm**
- Tubulocystic, papillary, or solid architecture with hyalinized stroma
- **Eosinophilic extracellular hyaline globules**

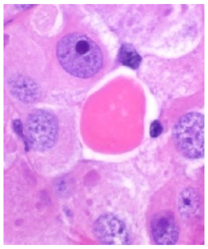

Monolayered cuboidal cells
Hob nailing

OTHER HIGH YIELD POINTS

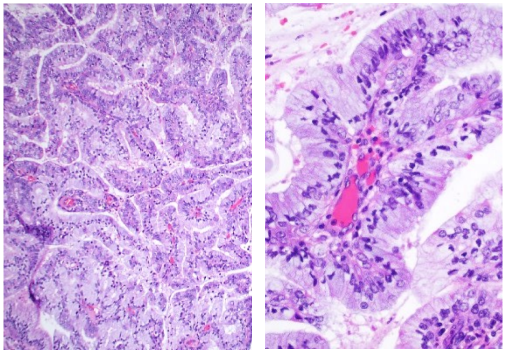
- Often post-menopausal women with vaginal bleeding
- Grading not applicable
- Relatively poor prognosis
- IHC: (+) HNF-1beta, NapsinA, p16 (patchy) (-) ER (usually); p53 can be wildtype, mutant, or aberrant (cytoplasmic expression)

Path Presenter


Pleomorphic nuclei


Eosinophilic globules

> 50% of cells mucinous component



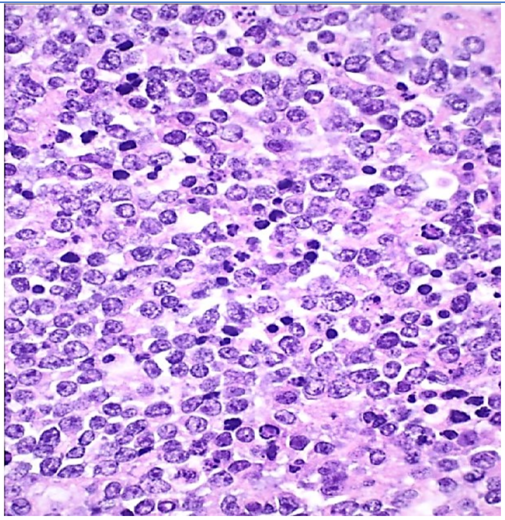
MUCINOUS CARCINOMA

MORPHOLOGY

- Endometrial carcinoma in which >**50% of the neoplasm is mucinous**
- **Often low-grade** with glandular or villoglandular architecture and uniform mucinous columnar cells with minimal stratification/atypia

OTHER HIGH YIELD POINTS

- Very rare, most tumors that are mucinous are endometrioid adenocarcinoma with mucinous differentiation, which can be graded using FIGO System
- **Frequent *KRAS* mutations** (somatic), relatively good prognosis
- **Be sure to consider endocervical origin on biopsy**
- Mucinous carcinoma of gastric/gastrointestinal type (new entity): glands with mucin which may contain goblet cells
- IHC: (+) CK7, MUC6, PAX8, CK20, CDX2; (+/-) ER



Monotonous, discohesive cells

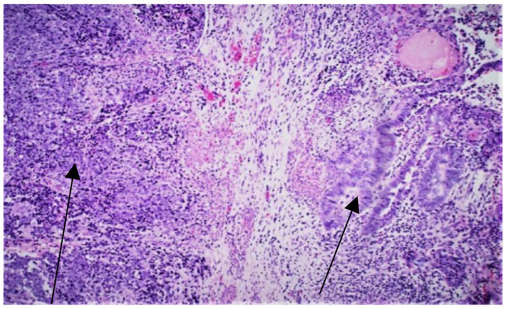
UNDIFFERENTIATED CARCINOMA

MORPHOLOGY

- Malignant epithelial neoplasm with **no differentiation**
- Sheets of medium-sized, relatively **uniform, monotonous, discohesive cells** with condensed chromatin
- **No gland formation**, numerous mitoses, may have a myxoid matrix
- Often **numerous tumor-infiltrating lymphocytes (TILs)**

OTHER HIGH YIELD POINTS

- Often form large, polypoid masses, **very aggressive**
- Molecular: **often MMR-deficient**, frequent mutations of SWF/SNF pathway including *SMARCA4*, *INI1* (more aggressive), or *ARID1A*, *ARID1B*
- IHC: Loss of MLH1/PMS2 (if MMR deficient), loss of BRG1 (if SMARCA4 mutation), loss/focal AE1/AE3, EMA, ER/PR, PAX8
- Differential diagnosis:
  - ➢ FIGO 3 endometrioid/solid pattern of serous (positive for PAX-8)
  - ➢ High-grade neuroendocrine carcinoma (>10% of cells positive for synaptophysin/ chromogranin)



Undifferentiated component

Low-grade endometrioid component

DEDIFFERENTIATED ENDOMETRIAL CARCINOMA

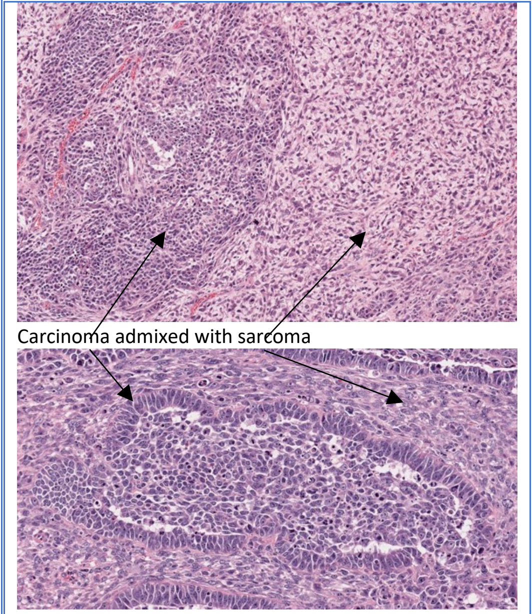
MORPHOLOGY

- **Two distinct components:**
  - ➢ Low-grade (FIGO 1-2) endometrioid carcinoma
  - ➢ High-grade undifferentiated carcinoma
- Each component has the IHC/molecular of that component

OTHER HIGH YIELD POINTS

- **Very aggressive**
- IHC: Very focal, often perinuclear dot-like EMA and AE1/AE3 (may be negative for AE1/AE3, so use a panel to confirm epithelial origin) PAX-8 (focal), ER/PR(-), *SMARCA4* (BRG1) IHC loss (1/3 or cases)

Path Presenter



Carcinoma admixed with sarcoma

CARCINOSARCOMA

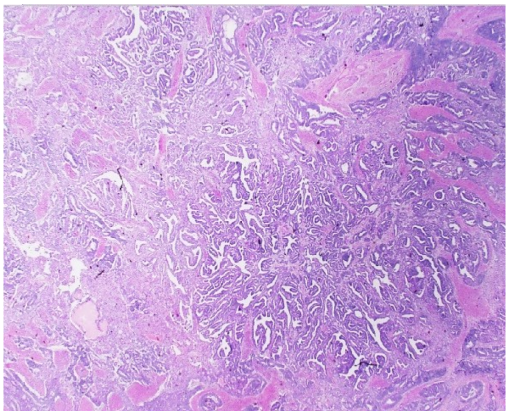
MORPHOLOGY

- **Biphasic tumor**:
  - ➢ **High-grade carcinoma** (epithelial)
  - ➢ **Sarcoma** (mesenchymal)
- Carcinoma is often **serous or endometrioid carcinoma**
- Sarcoma is often high-grade non-specific sarcoma, but "**heterologous" elements** can be seen, including rhabdomyosarcoma, chondrosarcoma, and osteosarcoma (which look/stain like they do elsewhere)
- Often intimate admixture of carcinoma and sarcoma elements

OTHER HIGH YIELD POINTS

- Typically, **post-menopausal women** presenting with vaginal bleeding
- It may be associated with tamoxifen use, pelvic radiation
- Often a **large pelvic mass that prolapses** out of the cervix in ~1/2 of cases
- Molecular: Frequent *TP53* mutations
- **Poor prognosis** (especially if higher stage, > 5 cm, and sarcomatous predominance), frequent pelvic recurrences, and lymph node metastases (carcinomatous component)

Path Presenter



Mesonephric like carcinoma

MESONEPHRIC-LIKE CARCINOMA

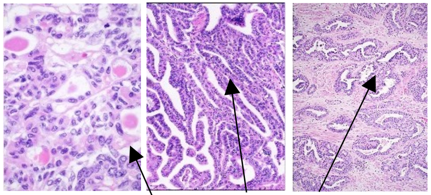
MORPHOLOGY

- Small glands/ tubules with **eosinophilic colloid-like material**, papillary, ductal, retiform, solid, or spindle architecture
- Moderate nuclear atypia with vesicular nuclei

Path Presenter

OTHER HIGH YIELD POINTS

- IHC: (-) ER/PR, TTF-1
  (+) GATA-3 CD10
  (+/-) calretinin
- Wild type p53
- *KRAS* mutation with gain of 1q

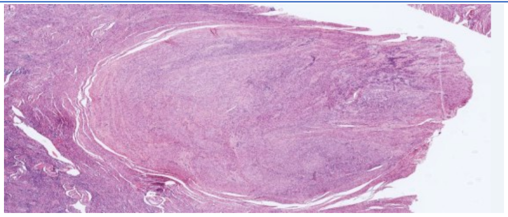


Tubules with duct like architecture

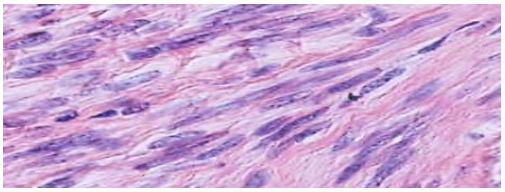
Retiform/slit-like architecture

Colloid like material

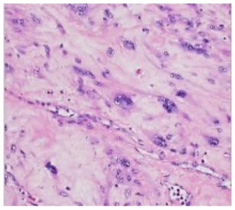
MESENCHYMAL TUMORS OF THE UTERUS



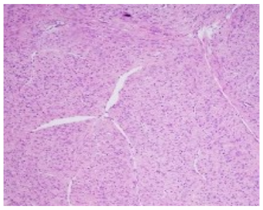
Well circumscribed, whorled mass



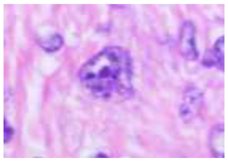
Cigar-shaped nuclei, eosinophilic fibrillary cytoplasm



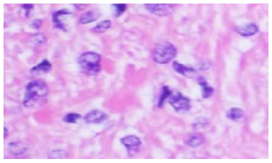
Bizarre nuclei



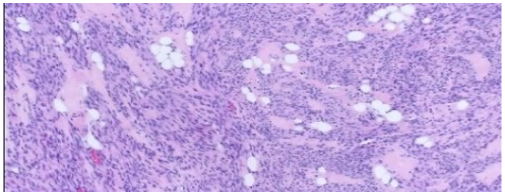
Fumarate hydratase deficient



Eosinophilic nucleoli with halo



Rhabdoid inclusions



Lipoleiomyoma

UTERINE LEIOMYOMA

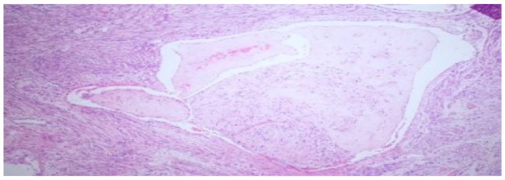
MORPHOLOGY

- Single/multiple with firm **whorled cut surface**, soft (cellular/epithelioid variant), yellow (lipoleiomyoma), beefy red (red degeneration in pregnancy), hemorrhagic foci (progesterone therapy; apoplectic change)
- **Well circumscribed/unencapsulated**
- **Spindle cells with indistinct borders**, eosinophilic fibrillary cytoplasm in **intersecting fascicles**
- **Cigar-shaped nuclei** (blunt at one end, tapering at the other), small nucleoli
- Rare mitosis, thick-walled blood vessels

OTHER HIGH YIELD POINTS

- **Benign** smooth muscle tumor
- **Most common uterine tumor**
- IHC: (+) desmin, SMA, caldesmon
- Variants:
  - **Cellular leiomyoma** – increased cellularity
  - **Leiomyoma with bizarre nuclei**—smudged, hyperchromatic, pleomorphic nuclei; no mitoses, no tumor necrosis
  - **Mitotically active leiomyoma**—increased mitoses (6-10/HPF), no atypia or tumor necrosis
  - **Fumarate hydratase (FH) deficient leiomyoma -** staghorn vessels, eosinophilic nucleoli with halos, and rhabdoid inclusions; most cases are due to sporadic mutation but may be associated with hereditary leiomyomatosis & renal cell carcinoma (HLRCC) syndrome
  - **Hydropic leiomyoma** –prominent edema
  - **Apoplectic leiomyoma** – due to progesterone treatment (stellate zones of hemorrhage and infarct type necrosis)
  - **Lipoleiomyoma** – mixture of smooth muscle and mature adipocytes
  - **Myxoid leiomyoma** – hypocellular myxoid stroma, no atypia/mitosis
  - **Epithelioid leiomyoma** – round/polygonal cells with eosinophilic, granular, or clear cytoplasm; no atypia, rare mitosis (< 2/10 HPF)
  - **Diffuse leiomyomatosis** – innumerable poorly circumscribed tumors

Link Link



INTRAVENOUS LEIOMYOMATOSIS

MORPHOLOGY

- Intravascular growth of benign smooth muscle cells resembling leiomyoma

OTHER HIGH YIELD POINTS

- Extrauterine extension into veins, can rarely extend to the heart or pulmonary veins, leading to sudden death

SMOOTH MUSCLE TUMOR OF UNCERTAIN MALIGNANT POTENTIAL ("STUMP")

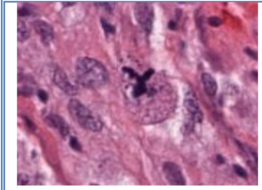
MORPHOLOGY

- Smooth muscle tumor whose features preclude a definitive diagnosis of leiomyoma vs. leiomyosarcoma
- Often with either equivocal mitoses or necrosis

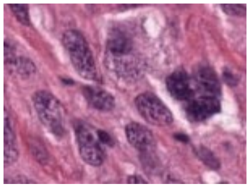
OTHER HIGH YIELD POINTS

- Relatively low risk of recurrence

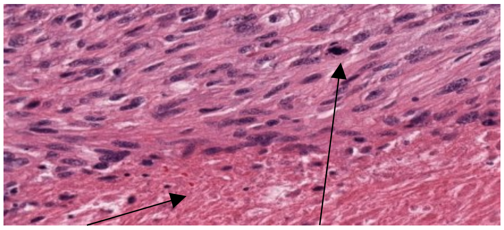
Path Presenter



Atypical mitosis



Cytologic atypia



Necrosis Mitosis

LEIOMYOSARCOMA

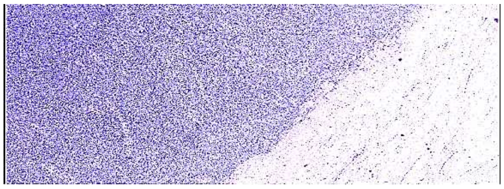
MORPHOLOGY

- Typically **spindle cell**, but can be epithelioid or myxoid
- Malignant features include:
  - **High-grade cytologic atypia**
  - **Increased mitoses** (typically >10/10 HPF)
  - **Tumor-type necrosis** with abrupt transition

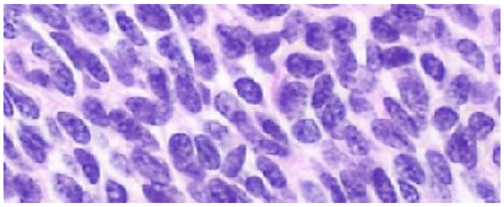
OTHER HIGH YIELD POINTS

- **Malignant** smooth muscle tumor
- Genetically complex chromosomal aberrations with high indices
- Molecular: *TP53, RB1, ATRX,* and *HMGA2* mutations
- **Very poor prognosis**

Path Presenter



Well circumscribed



Monotonous cells, round/oval nuclei, scant cytoplasm

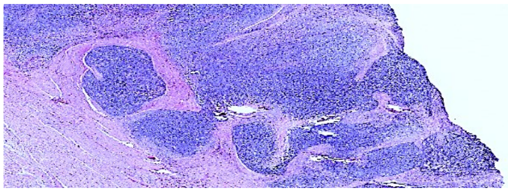
ENDOMETRIAL STROMAL NODULE

MORPHOLOGY

- Relatively **well-circumscribed** margin
- Diffuse proliferation of **monotonous blue cells** resembling proliferative phase of endometrial stroma
- Uniform round-ovoid nuclei, scant-moderate eosinophilic cytoplasm
- ESN may demonstrate focal **finger-like projections toward the myometrium**
- **To confirm ESN diagnosis**, the projections should be < 3 in number and <3mm in their maximum extension

OTHER HIGH YIELD POINTS

- Benign tumor
- IHC: (+) vimentin, CD10, ER, PR
- t(7;17) (p15;q21) – *JAZF1-SUZ12* fusion (50% of ESNs)



Tongue like invasion

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

MORPHOLOGY

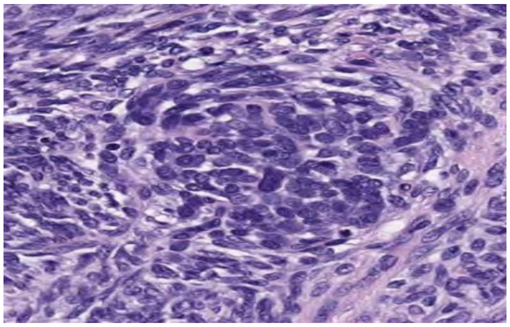
- A malignant tumor composed of cells resembling proliferative endometrial stroma with infiltrative growth Often have "tongue-like" growth

OTHER HIGH YIELD POINTS

- t(7;17) (p15;q21) – *JAZF1-SUZ12* fusion
- Intermediate prognosis

Path Presenter

Link Link



High-grade round cell and spindle cell morphology

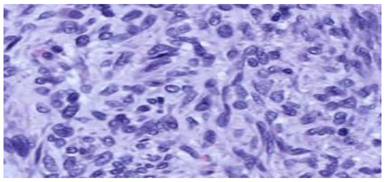
HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

MORPHOLOGY

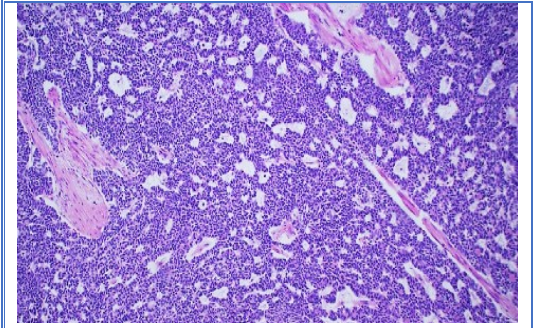
- Malignant tumor derived from endometrial stromal cells with **high-grade round cell morphology**
- Frequently **myxoid**
- Typically confluent, permeative & **destructive** growth
- **Usually high mitotic activity, necrosis, and LVI**

OTHER HIGH YIELD POINTS

- Molecular: *YWHAE*-, *BCOR*-associated fusions, or *BCOR* ITD



Myxoid areas with high grade cells



Resembles ovarian sex cord tumor

UTERINE TUMOR RESEMBLING OVARIAN SEX CORD TUMOR ("UTROSCT")

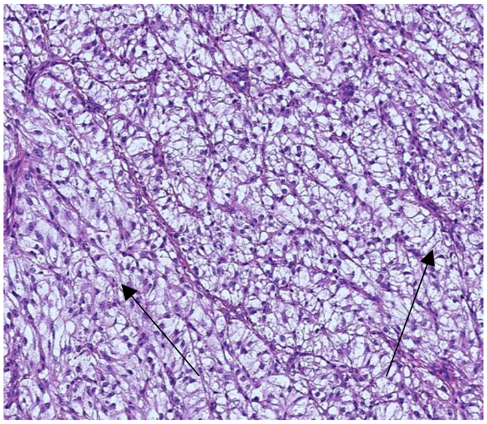
MORPHOLOGY

- Well-circumscribed neoplasm **resembling ovarian sex cord tumor** without endometrial stromal component

OTHER HIGH YIELD POINTS

- **Benign** course typically
- IHC: (+) WT-1, (+/-) Inhibin, calretinin, and Melan-A
- Recurrent ***NCOA2/3* translocations**

Path Presenter



Epithelioid cells with clear cytoplasm delicate vasculature

PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA)

MORPHOLOGY

- **Epithelioid cells** with clear to eosinophilic cytoplasm demonstrating **melanocytic and smooth muscle differentiation**

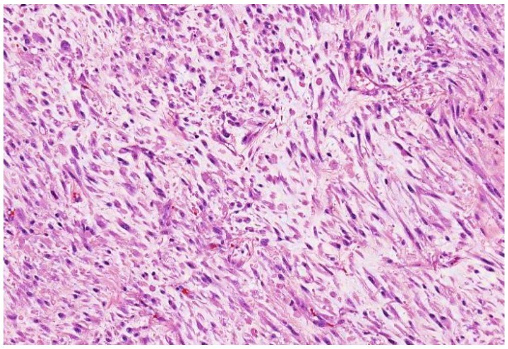
OTHER HIGH YIELD POINTS

- IHC: (+) HMB45, Melan-A, Cathepsin K; variable smooth muscle markers
- Some have ***TFE3* fusions** → clear nested epithelioid morphology
- **Features to evaluate malignancy:**

1) ≥ 5cm, 2) High-grade atypia, 3) >1 mitoses/50HPF, 4) Necrosis, 5)LVI

- ➢ <3 of above features → Benign/Uncertain malignant potential
- ➢ ≥3 of above features → Malignant

Link Link



Spindled to polygonal cells, myxoid stroma

INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMT)

MORPHOLOGY

- Spindled to polygonal cells growing in **fascicles**, often have **myxoid stroma**

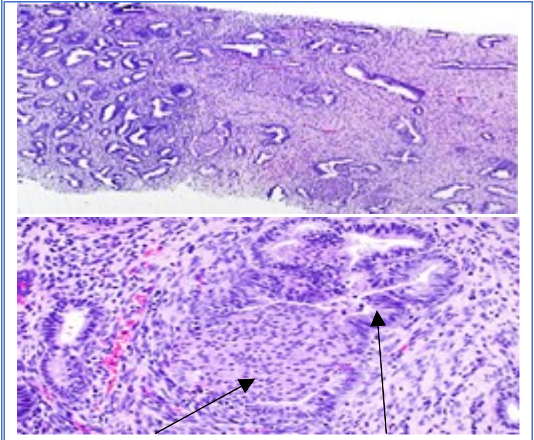
OTHER HIGH YIELD POINTS

- IHC: **(+) ALK1**; variable smooth muscle markers
- Molecular: **ALK rearrangements**
- **Features that predict aggressive behavior**: size > 7cm, necrosis, moderate to severe cytologic atypia, mitoses, LVI

Path Presenter

15. GYNECOLOGIC PATHOLOGY

MIXED EPITHELIAL AND MESENCHYMAL UTERINE TUMORS



Squamous morular metaplasia Architectural complexity

ATYPICAL POLYPOID ADENOMYOMA

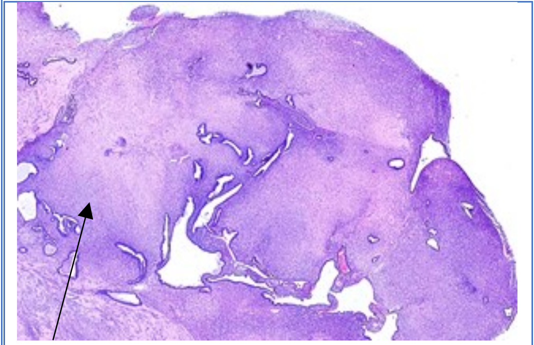
MORPHOLOGY

- **Three key features:**
    - Endometrial glands with **architectural complexity and cytologic atypia**
    - Prominent **squamous morules**
    - Surrounding prominent **cellular fibromuscular stroma**

OTHER HIGH YIELD POINTS

- Often centered in the **lower uterine segment**
- Associated with **MLH-1 promoter methylation** (~50%)
- Can be confused with myoinvasive endometrioid adenocarcinoma, **but APA fibromuscular stroma is p16+** (desmoplastic stroma/myometrium is p16-)
- **Benign**, but can progress to atypical hyperplasia/EIN or adenocarcinoma

Path Presenter



Cellular stroma with leaf–like architecture

ADENOSARCOMA

MORPHOLOGY

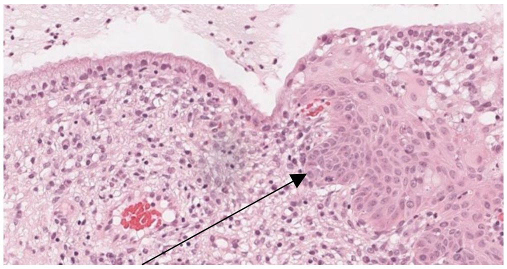
- **Mixed epithelial and mesenchymal tumor** with a benign epithelial component and stroma is low-grade malignant (think phyllodes tumor)
- Papillary/polypoid projections of cellular stroma (often with condensation, **"cuffing" around glands**)
- Can show heterologous elements and sarcomatous overgrowth

OTHER HIGH YIELD POINTS

- *MDM2/CDK4* and *TERT* gene amplifications

Path Presenter

CERVIX



Squamous metaplasia within an endocervical polyp

SQUAMOUS METAPLASIA

MORPHOLOGY

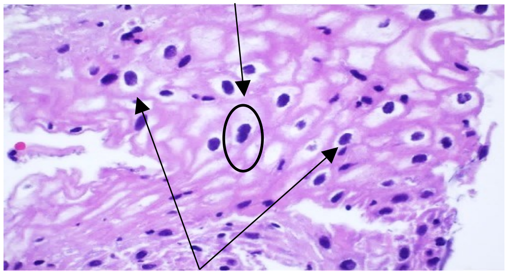
- Uniform chromatin, minimal nuclear contour irregularities, and more likely to have **residual mucinous epithelium** than SIL
- Features can mimic LSIL/HSIL

OTHER HIGH YIELD POINTS:

- **IHC: (-) p16**

Path Presenter

Binucleate Koilocyte

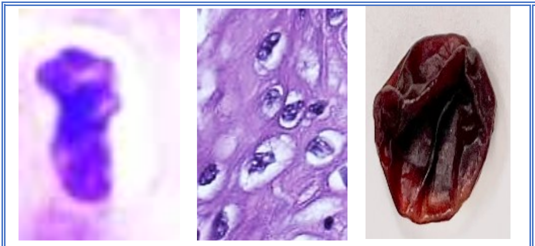


Koilocytes

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL)

MORPHOLOGY

- Proliferation of hyperchromatic basal-like cells that extends **less than 1/3** of the way up the epithelium
- Cells differentiate (gain cytoplasm) in upper epithelium
- **Mitoses confined to lower zone**
- Many nuclei are **hyperchromatic** with irregular nuclear contours (at all levels)
- **Koilocytes** = large superficial cells with perinuclear halos and large, irregular, "raisinoid" nuclei; can be **binucleated**

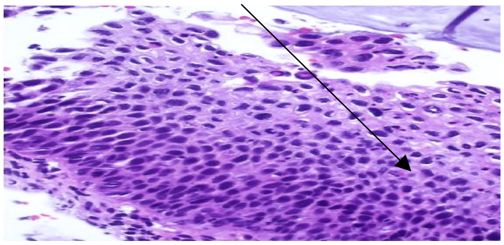


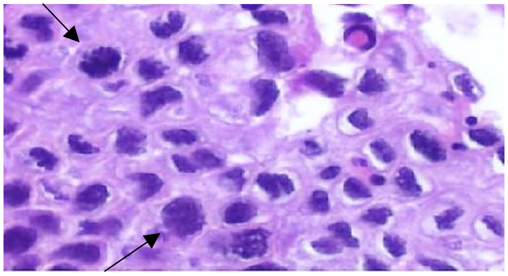
Koilocyte: large, irregular nuclear membrane (“raisinoid”)

Link Link

OTHER HIGH YIELD POINTS

- **Intraepithelial** (in situ, non-invasive), squamous dysplasia due to **Human Papilloma Virus (HPV) infection**
- Sexually transmitted disease
- **HPV 16 & 18** most associated with HSIL/SCC
- **HPV 6 & 11** most associated with LSIL/condylomas
- Usually infects the transition zone between squamous and glandular mucosa
- HPV can infect epithelium without integrating into the nucleus, creating LSIL/condyloma (often transient, self-limited) or integrate, where viral serotypes have oncogene overexpression that drives clonal production of epithelial cells
- **HPV-associated oncoprotein E6 inactivates p53, E7 inactivates Rb**
- **Often spontaneously regresses**, so just observed clinically
- **Condyloma** – grossly evident morphological variant of LSIL, often composed of papillary fronds





HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

MORPHOLOGY

- Proliferation of hyperchromatic basal-like cells that extend at least 2/3 of the epithelium (CIN2) or full-thickness (CIN3/CIS) of the epithelium
- Cells have enlarged, hyperchromatic nuclei with irregular nuclear contours and increased N:C ratios
- Little to no superficial maturation
- Mitoses are common at all levels, including atypical mitoses
- Nucleoli are unusual→ raise the possibility of inadequately sampled invasive carcinoma (p16+) or metaplasia (p16-)
- Variants:
  1) Keratinizing—abnormal surface keratinization
  2) Papillary—papillomatous architecture

OTHER HIGH YIELD POINTS

- Treatment: Given the risk of progression to SCC, often treated with LEEP, laser ablation, cryotherapy, or surgical conization
- IHC: p16 (used as a surrogate marker of High-risk HPV infection)
- When to use p16 Immunohistochemistry → morphologic DDX is between HSIL (p16 +) and a mimic, such as squamous metaplasia (p16 -)

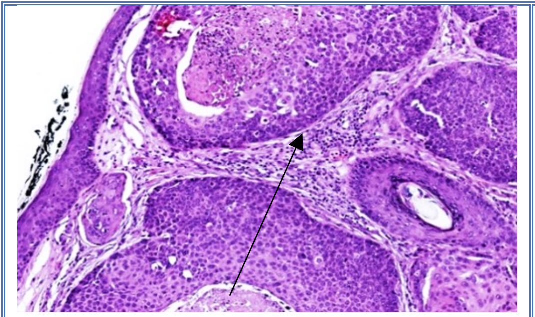
SQUAMOUS CELL CARCINOMA

MORPHOLOGY

- Morphologically, most are non-keratinizing and basaloid
- Sheet-like growth with infiltrating bands and single cells
- Often desmoplastic/inflammatory stroma
- Can be keratinizing or non-keratinizing
- With invasion can see "paradoxical maturation" with increased cytoplasmic eosinophilia
- Several subtypes including keratinizing, non-keratinizing, basaloid, verrucous, papillary, and lymphoepithelioma-like

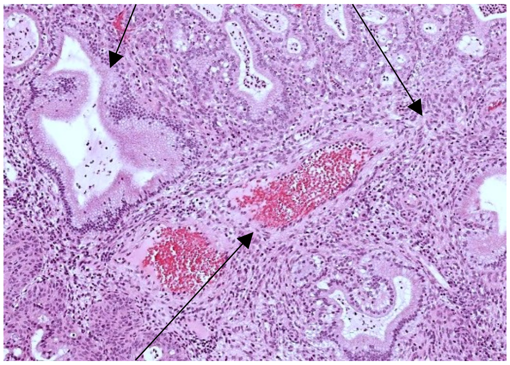
OTHER HIGH YIELD POINTS

- An invasive epithelial tumor composed of squamous cells of varying degrees of differentiation
- Virtually all associated with HPV infection, most commonly types 16 or 18, and arise from HSIL-precursor lesion
- Worldwide, 2nd or 3rd most common cancer in women, mostly in low-resource countries, without cervical cancer screening programs (Pap smears)
- In the US, rates have dropped dramatically in recent history due first to screening and now to HPV immunizations
- Treatment depends on the stage but often involves chemoradiation
- Depth of tumor invasion is measured from the base of the HSIL origin (or nearest dysplastic epithelium if the site of origin is not apparent) to the deepest point of invasion
- Note: if tumors are severely ulcerated or largely exophytic, measuring the depth of invasion may be hard/impossible



Often desmoplastic/inflammatory stroma

	Invasive SCC	HSIL colonization of endocervical glands
Paradoxical maturation **High N:C ratio HSIL cells to invasive cells with abundant cytoplasm**	Present	Absent
Stromal reaction: edema, desmoplasia +/- inflammation	Present	Absent
Nest contours	Irregular (angulated)	Rounded
Anastomosing nests of atypical cells	Present	Absent
Nearby uninvolved glands	Absent	Present



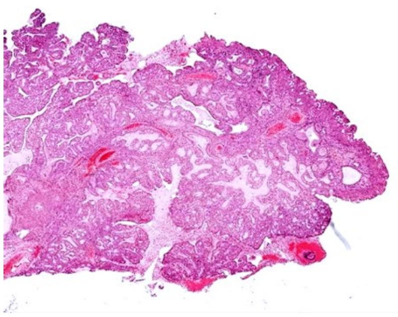
ENDOCERVICAL POLYP

MORPHOLOGY

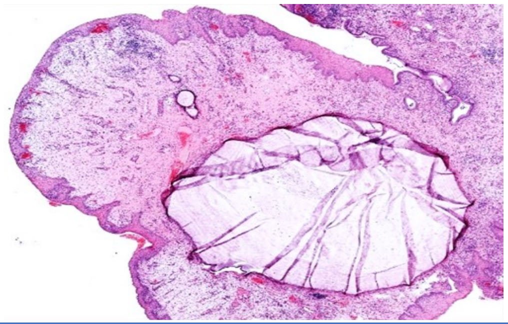
- **Focal hyperplastic protrusions** of benign endocervical glands and **loose fibrous stroma**
- **Cystic changes of glands**
- Frequently associated inflammation
- It may have **surface squamous metaplasia**

OTHER HIGH YIELD POINTS

- **Most common benign growth of the cervix**



Path Presenter



NABOTHIAN CYST

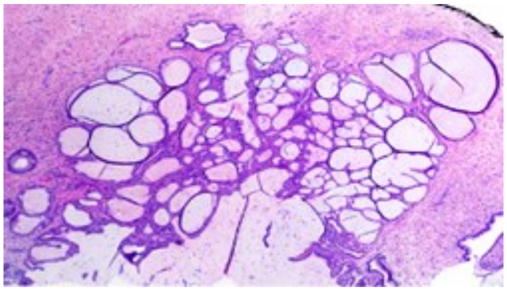
MORPHOLOGY

- **Endocervical gland dilation** after outlet obstruction
- **Grossly dilated cysts** filled with **translucent mucoid material**
- Lined by a single layer of **columnar mucinous endocervical** epithelium, but may be flattened due to atrophy

OTHER HIGH YIELD POINTS

- Common, non-neoplastic, usually incidental, and asymptomatic

Path Presenter



TUNNEL CLUSTER

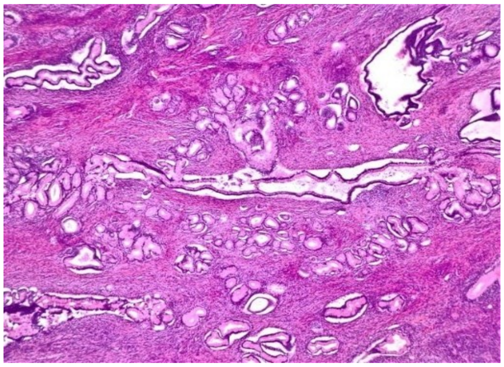
MORPHOLOGY

- **Clusters of benign endocervical glands** are often near the surface
- Can be cystically dilated
- **Main importance—can be confused with minimal deviation adenocarcinoma** (but in contrast, tunnel clusters are superficial and have no atypia or mitotic activity)

OTHER HIGH YIELD POINTS

- Benign, common, incidental

15. GYNECOLOGIC PATHOLOGY



Lobular Endocervical Glandular Hyperplasia (LEGH)
Courtesy: Miruna Popescu, MD (@MirunaPopescu13)

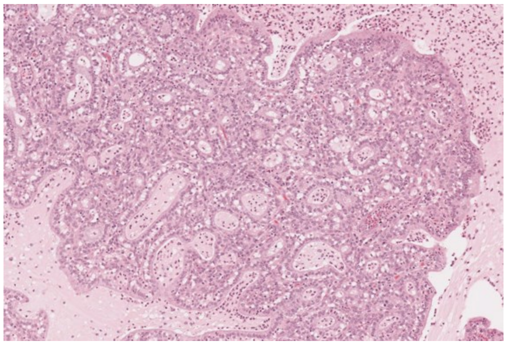
ENDOCERVICAL GLANDULAR HYPERPLASIA

MORPHOLOGY

- Confined to the **inner 1/3–1/2 of the cervical wall** with no mitoses or atypia
- **Lobular Endocervical Glandular Hyperplasia (LEGH)**
  - Proliferation of tightly packed small endocervical glands in a lobular pattern, resembling gastric pyloric gland epithelium
- **Diffuse Laminar Endocervical Glandular Hyperplasia (DLEG)**
  - Proliferation of tightly packed, small to medium-sized endocervical glands, no lobular architecture but has a clearly defined base

OTHER HIGH YIELD POINTS

- Rare
- LEGH is thought to be the precursor lesion to gastric-type/minimal deviation adenocarcinoma



Tightly packed glands/tubules

MICROGLANDULAR HYPERPLASIA

MORPHOLOGY

- **Tightly packed glands/tubules** lined by flattened to cuboidal cells with eosinophilic cytoplasm, sometimes a small mucin vacuole
- **Uniform small nuclei** with rare mitoses
- Florid cases can have **reticular ("net-like") or solid growth** & increased atypia
- **No invasive growth**, often associated with inflammation

OTHER HIGH YIELD POINTS

- **Benign, very common**
- IHC: p63 highlights a subset of the cells, ER/PR (+), vimentin (-)

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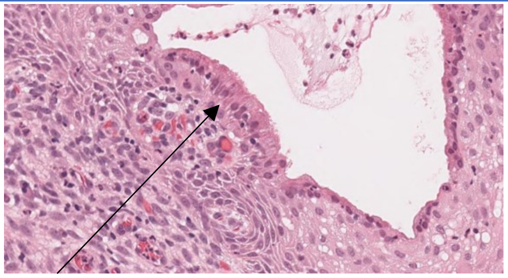

Ciliated tubal-type epithelium

TUBAL METAPLASIA

MORPHOLOGY

- Endocervical glandular epithelium **replaced by tubal epithelium, which is ciliated with intercalated "peg" cells**
- No mitoses, no significant atypia, should be one cell layer thick

OTHER HIGH YIELD POINTS

- **Main significance—can be confused with AIS**

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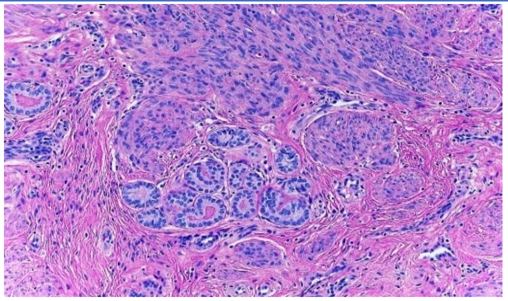


Small tubules/cysts arranged in clusters (Image courtesy of Frank Ingram, MD)

MESONEPHRIC REMNANT

MORPHOLOGY

- **Small tubules/cysts** deep within the wall of the cervix, often arranged in **clusters**
- Tubules are lined by cuboidal cells and have **characteristic central pink PAS-positive secretions**
- **If large collection→ Mesonephric hyperplasia** (still maintains lobular growth)

OTHER HIGH YIELD POINTS

- **Benign vestigial embryologic remnants** from the mesonephric duct
- Most common in the **lateral aspect of the cervix**
- IHC: (+) GATA-3, TTF-1; (-) p16, ER

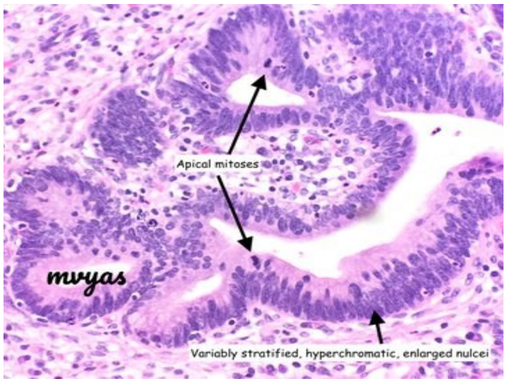


Image courtesy of Monica Vyas, MD

ENDOCERVICAL ADENOCARCINOMA IN SITU (AIS)

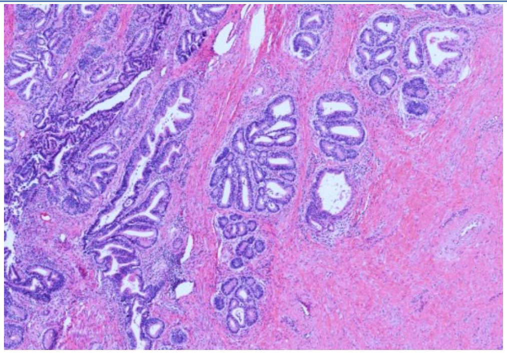
MORPHOLOGY

- **Glands with cell crowding and pseudo-stratification** of hyperchromatic nuclei
- **Depletion of intracytoplasmic mucin**
- **Apical mitoses, apoptotic debris,** maintained lobular architecture
- **Stratified mucin-producing intraepithelial lesion (SMILE):**
  - Stratified epithelium with nuclear atypia, hyperchromasia, and mitotic figures; mucin vacuoles at all cell layers

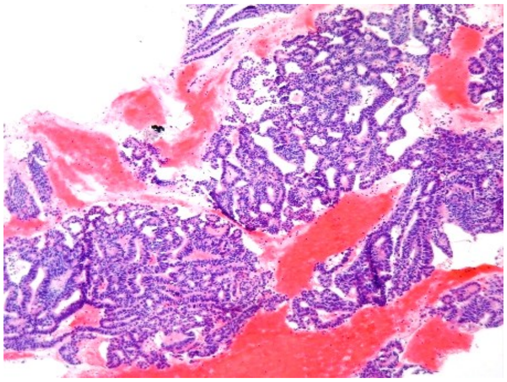
OTHER HIGH YIELD POINTS

- **Non-invasive adenocarcinoma**, confined to pre-existing glandular epithelium
- Caused by **high-risk HPV**, classically type 18 – often nearby HSIL
- IHC: **p16 diffuse/strong positive**, loss of ER/PR, elevated Ki67

Link Link



Haphazard extension of glands



Cribriform to papillary architecture, mucin poor, pseudostratified, hyperchromatic nuclei

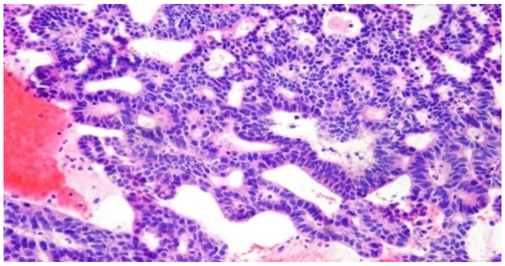


Image courtesy of Khanh Ho, MD (@Ho_Khanh_MD)

ENDOCERVICAL ADENOCARCINOMA, USUAL TYPE

MORPHOLOGY

- Well to moderately differentiated **cribriform to papillary architecture**
- **Characteristic morphology** with mucin-poor glands; pseudostratified, enlarged, hyperchromatic nuclei; ± nucleoli
- **Must have signs of definite invasion:**
  - **Complex architecture**
  - **Haphazard growth**
  - Extension of glands beyond the depth of normal endocervical glands, especially if **near thick-walled blood vessels**
  - **Stromal reaction** (edema, chronic inflammation, or desmoplasia)

OTHER HIGH YIELD POINTS

- **Most common** type of endocervical adenocarcinoma (~90%)
- An **HPV16/18** mediated **(IHC: p16 +)** invasive adenocarcinoma of the cervix
- Often presents with vaginal bleeding and a mass
- Maybe exophytic or ulcerated architecture

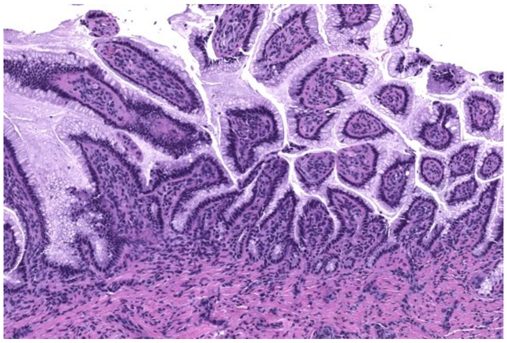
	Subtypes	Morphology
HPV positive	Usual type Mucinous Villoglandular	Apical mitosis and apoptosis are identified easily at scanning magnification
HPV negative	Gastric Clear cell Mesonephric Endometroid Serous	Diverse histology

Patterns of invasion of endocervical adenocarcinoma

Silva Group	Morphology	Risk	Treatment
A	Well demarcated glands with rounded contour, No single cells, no LVI, no solid growth	Low	LN sampling is not needed
B	Localized destructive stromal invasion (No solid growth, LVI +/-)	Intermediate	Sentinel LN sampling
C	Diffuse destructive stromal invasion	High	Nodal resection

Path Presenter

15. GYNECOLOGIC PATHOLOGY


Gastric-type endocervical adenocarcinoma

ENDOCERVICAL ADENOCARCINOMA, GASTRIC TYPE

MORPHOLOGY

- Diffuse, **deeply infiltrating glands** in the stroma with a desmoplastic response
- Cells with **abundant pale to eosinophilic cytoplasm**, distinct cell borders
- Round, vesicular nuclei, often with **prominent nucleoli**

OTHER HIGH YIELD POINTS

- **Gastric type is not related to high-risk HPV; poor prognosis**
- Typical presentation: **profuse watery discharge, "barrel-shaped" cervix**
- IHC: (-) p16, ER/PR; (+) PAX8, CK7, HNF-1β, NapsinA
- Precursor lesion: LEGH, associated with Peutz-Jegher's syndrome
- Prognosis: significantly worse than usual-type adenocarcinoma

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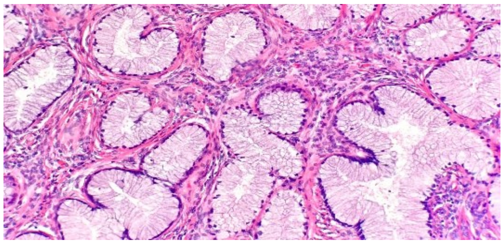
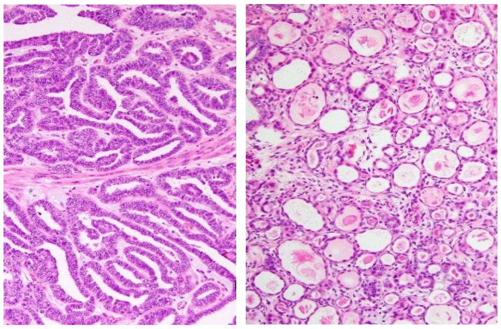

Minimal deviation (adenoma malignum)

MINIMAL DEVIATION (ADENOMA MALIGNUM)

- **Highly differentiated form of gastric-type adenocarcinoma**
- Can be difficult to diagnose due to highly differentiated morphology
- Numerous **deeply invasive** haphazard, deceptively bland glands, which often **lack surrounding stromal desmoplasia**
- Intraglandular papillary protrusions and irregular profiles
- Focally, **some glands display malignant cytologic features** (vesicular nuclei, prominent red nucleoli) with stromal desmoplasia

Tubular architecture Eosinophilic secretions


Images courtesy of Kyle Devins, MD (@md_kyle)

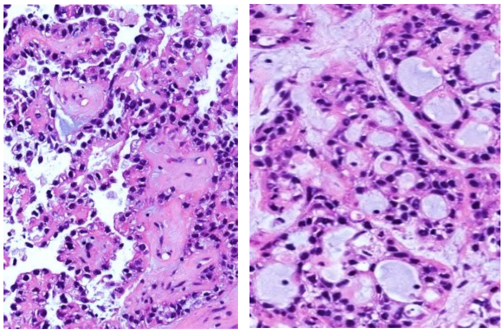
MESONEPHRIC ADENOCARCINOMA

MORPHOLOGY

- **Variable architectural patterns**: tubular, papillary, etc.
- **Small, tightly packed glands** with low-cuboidal cells with **eosinophilic PAS-D positive secretions**
- Relatively **bland, uniform cytology**

OTHER HIGH YIELD POINTS

- Rare, develop from **mesonephric remnants**
- Often located **deep in lateral cervical stroma**
- IHC (similar to mesonephric remnants): (+) PAX8, GATA-3, luminal CD10; (+/-) TTF-1(+/-); (-) p16, ER, PR


Papillary architecture Hyperchromatic cells

CLEAR CELL CARCINOMA

MORPHOLOGY

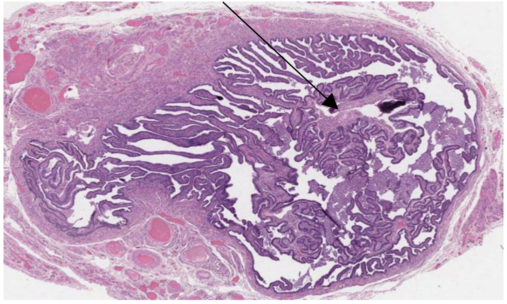
- Abundant clear to granular eosinophilic cytoplasm with frequent "hobnail" appearance, intracytoplasmic hyaline globules
- Large, hyperchromatic, pleomorphic nuclei
- Solid, cystic, or papillary architecture

OTHER HIGH YIELD POINTS

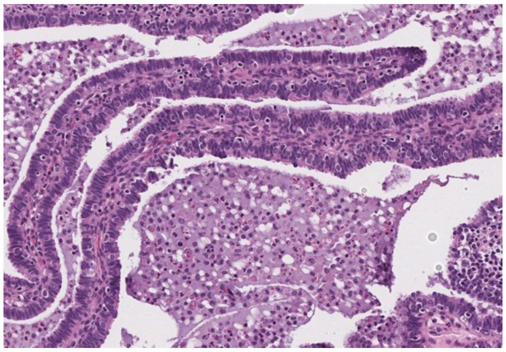
- **NOT associated with high-risk HPV**
- Associated with **diethylstilbestrol (DES) exposure**
- If DES-exposure related, tumor arises from ectocervix
- If non-DES related, tumor arises from the endocervix or ectocervix
- IHC: (+) HNF-1β, NapsinA; (+/-) p16
  (-) ER/PR; p53 wildtype

FALLOPIAN TUBE

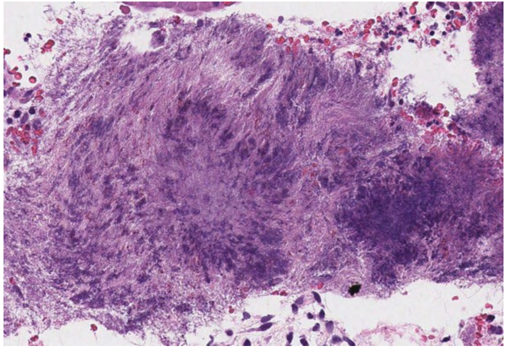
Fallopian tube with purulent exudate



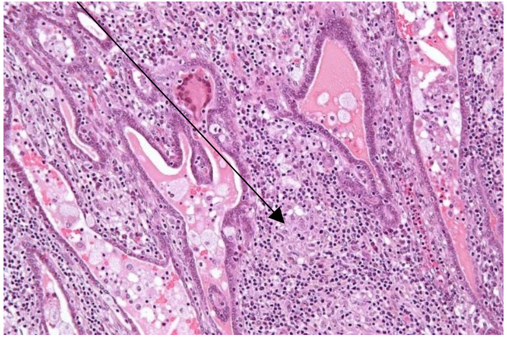
Mixed acute & chronic salpingitis



Actinomycotic (sulfur) granules



Granulomatous salpingitis

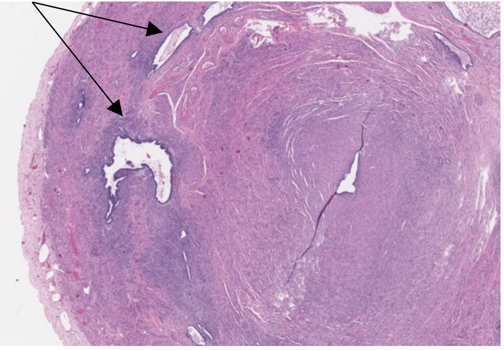


Courtesy of Michael Bonert, MD, FRCPC via Wikimedia

PELVIC INFLAMMATORY DISEASE (PID)

- **Acute salpingitis**
  - Acute inflammation of fallopian tube mucosa
- **Follicular salpingitis**
  - If the lumen of the tube/ostium remains open, tubal contents are released into the peritoneal cavity
  - Damaged plicae fuse with each other, forming a network of compartmentalized, epithelial-lined spaces or "follicle-like" areas (**Note**: *Nothing to do with lymphoid follicles!*)
- **Hydrosalpinx follicularis**
  - Expansion of tube due to **accumulation of fluid**; may fuse with ovary mimicking serous ovarian tumors
- **Chronic salpingitis**
  - Dense **lymphoplasmacytic infiltrate**; fusion of plicae is uncommon
- **Tubo-ovarian abscess (TOA):**
  - Intense chronic inflammation causing tubo-ovarian adhesions and tubo-ovarian masses
- **Actinomycosis PID**
  - Associated with longstanding intrauterine device (IUD) use
  - Actinomycotic (sulfur) granules within the inflammatory exudate
- **Pyosalpinx**
  - When the tubal lumen gets closed during acute inflammation, **purulent exudate** accumulates with expansion of tube
- **Hydrosalpinx:**
  - Comes after pyosalpinx – purulent exudate gets reabsorbed and **clear fluid** is left behind with **quiescent inflammation** of the mucosa
  - Shape of the tube is like a "chemist's retort" (glassware with a spherical base and long, narrow neck)
  - Wall is thinned out with an attenuated smooth muscle layer, only few remaining plical folds
  - Flattened to normal epithelium
- **Granulomatous salpingitis**
  - Causes: tuberculosis (**most common**, although rare in the US), sarcoidosis, Crohn's disease, parasitic infection, foreign body
  - Route of infection: hematogenous or lymphatic (tuberculosis)
  - Morphology: usually bilateral, with **granulomas** within the plicae
- **Xanthogranulomatous salpingitis**
  - Associated with PID
  - Yellow, polypoid mucosal projections
  - Collection of **histiocytes** with abundant, foamy cytoplasm and **microvesicles of lipid**
- **Pseudoxanthogranulomatous salpingitis**
  - Also known as "melanosis tubae" or "pigmentosis tubae"
  - Associated with a **history of endometriosis**
  - Swollen fallopian tube with brown, polypoid mucosal projections
  - Collection of a pure population of **histiocytes** containing lipofuscin
- **Salpingitis isthmica nodosa (SIN)**
  - Seen in young women; associated with infertility, ectopic pregnancy
  - Nodular swelling, with a rubbery, light tan to pale yellow tissue interspersed with small cystic spaces

Glands within thickened smooth muscle wall (SIN)

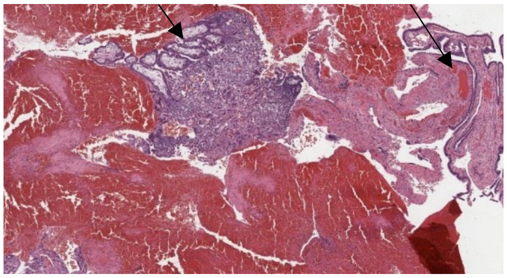


  - Microscopy: glands of various shapes and sizes embedded within hypertrophic smooth muscle of the tubal wall; may communicate with the original lumen
  - Absence of desmoplastic/inflammatory/edematous stromal reaction and bland nuclear features helps in **ruling out adenocarcinoma**, despite the appearance of glands embedded in stroma

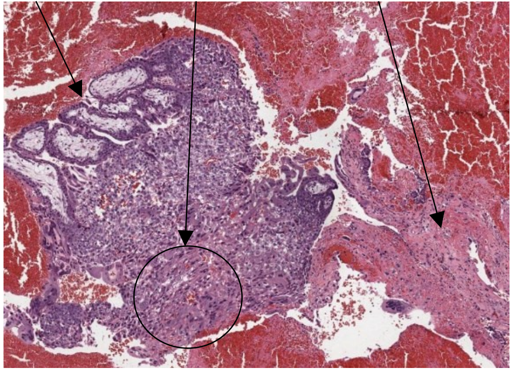
OTHER HIGH-YIELD POINTS

- **The clinical term of PID is equivalent histologically to salpingitis**
- Ascending infection from the vagina and cervix commonly due to:
  - *Neisseria gonorrhea, Chlamydia trachomatis, Mycoplasma genitalium*
- Seen in sexually active young women or in association with IUD
- Abdominal pain, fever, leukocytosis, dyspareunia, dysuria
- Complications: ectopic pregnancy, infertility, chronic pelvic pain

Blood and chorionic villi within dilated tubal lumen



Chorionic villi, syncytiotrophoblast, implantation site fibrin



ECTOPIC PREGNANCY

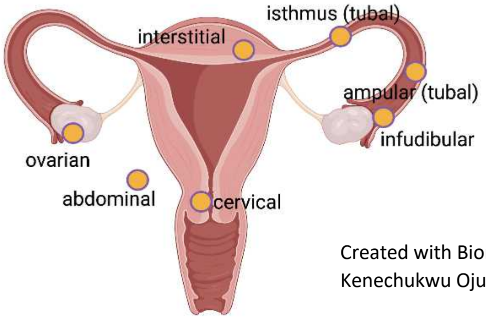
MORPHOLOGY

- Gross: sausage-like expansion of the ampullary segment of the fallopian tube, may see blood clots, chorionic villi, and/or embryo
- **Chorionic villi and/or extravillous trophoblast are required for diagnosis**
- Fetal tissue may be present; implantation site fibrin may be seen

OTHER HIGH-YIELD POINTS

- Accounts for ~2% of all pregnancies
- Complications: rupture → **obstetric emergency**
- Most common cause: idiopathic
- Most common site: **ampulla**
- Risk factors: PID, SIN, cigarette smoking, prior tubal surgery

Sites for ectopic pregnancy



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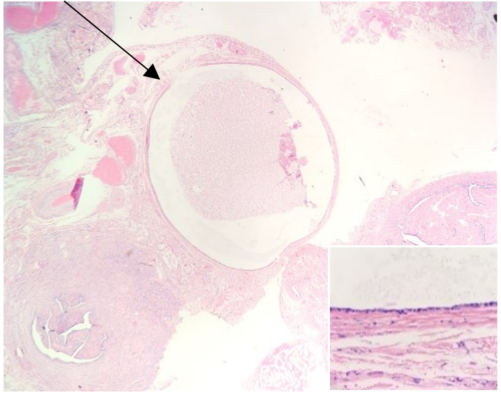
Paratubal cyst filled with serous fluid



Flat epithelial lining

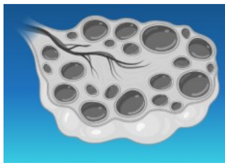
PARATUBAL CYST

MORPHOLOGY

- Simple cyst lined by cuboidal to flattened epithelial lining, located adjacent to the fallopian tube
- Differential diagnosis:
  - **Serous cystadenoma**: shows a) thicker wall that shows collagenized or compressed ovarian stroma, b) lack of plicae-like folds, which can sometimes be seen in paratubal cysts
  - **Hydrosalpinx**: shows a) paper-thin wall with limited amount of smooth muscle, b) typical gross appearance of a dilated and distorted fallopian tube, unlike a separate cystic mass of a paratubal cyst

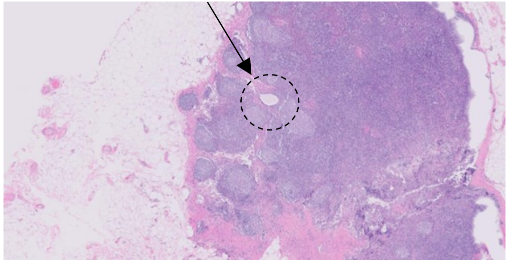
OTHER HIGH-YIELD POINTS

- Three types: paramesonephric (Mullerian, most common), mesothelial, and mesonephric (Wolffian)
- Hydatid of Morgagni: **most common paramesonephric cyst** (unrelated to parasitic hydatid cyst), attached to one of the fimbriae, tubal epithelium

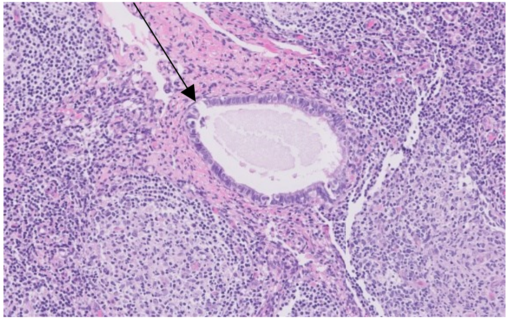


15. GYNECOLOGIC PATHOLOGY

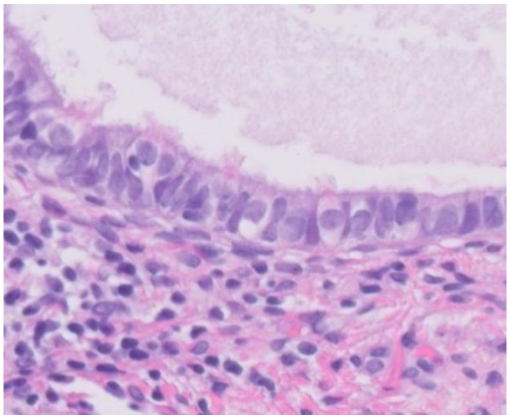
Lymph node with endosalpingiosis



Tubal-type epithelium entrapped in lymph node



Tubal epithelium showing ciliated columnar cells



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ENDOSALPINGIOSIS

MORPHOLOGY

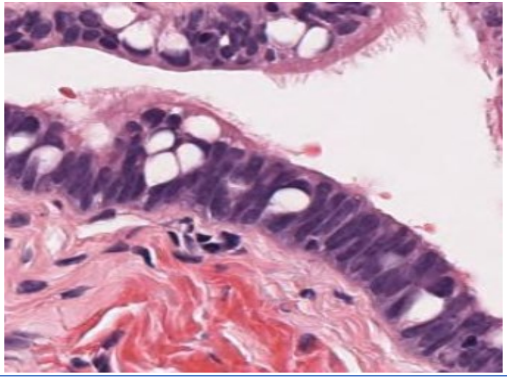
- Presence of **tubal-type epithelium** within peritoneal tissues, omentum, and/or regional lymph nodes
- Can be seen as multiple, punctate, white to yellow, translucent to opaque fluid-filled cysts imparting a **vesicular or granular appearance** to the involved surface
- Multiple, simple glands lined by a single layer of tubal type epithelium
- Three cell types of fallopian tube (ciliated cells, secretory cells, and dark rod-like intercalated cells) in varying numbers, ± psammoma bodies
- Cells have prominent luminal margins, distinct borders, and basal nuclei
- PAS staining shows intact basement membrane surrounding each gland
- **Burned-out endosalpingiosis:** psammoma bodies found intermixed with subserosal fibrous tissue in the absence of associated epithelial elements
- **Atypical endosalpingiosis:** cellular stratification including cellular buds, cribriform pattern, varying degrees of cellular atypia, in the absence of a serous borderline malignancy
- Differential diagnosis:
    - **Mesothelial remnants**: located deeper than endosalpingiosis, show a collar of smooth muscle and lack of ciliated cells
    - **Serous borderline tumor vs. endosalpingiosis** (see table below)

OTHER HIGH-YIELD POINTS

- Also known as **benign Mullerian glandular inclusions** or Mullerian inclusion cysts
- Age group = reproductive age, mean age = 29
- Found in 10-15% of pelvic lymph node dissections and surgically removed omentum
- Associated with inflammatory tubal disease and epithelial ovarian tumors
- Origin: secondary Mullerian system or dislodged fimbrial cells
- Clinical features: asymptomatic, incidental finding

ENDOSALPINGIOSIS	SEROUS BORDERLINE TUMOR
Located within the lymph node capsule	Subcapsular location
Architecturally simple glands	Glands show complex architecture
Mitotically inactive	Mitotically active
Bland nuclear features	Nuclear atypia
Show distinct types of cells	Clonal proliferation

Nuclear crowding, high N:C, hyperchromasia

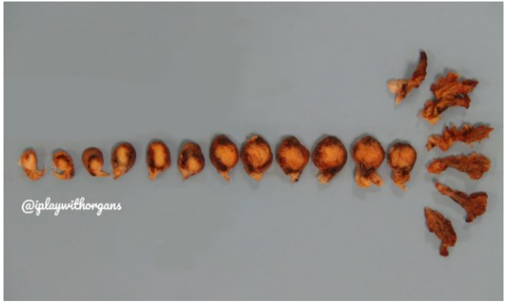


SEROUS TUBAL INTRAEPITHELIAL CARCINOMA (STIC)

MORPHOLOGY

- **Cytologic atypia** in the epithelial lining:
    - Epithelial stratification
    - High N:C ratio with nuclear enlargement, pleomorphism, and hyperchromasia
    - Prominent nucleoli
    - Absence of ciliated cells
- By definition, **absence of stromal invasion**

SEE-FIM protocol



Courtesy of Corey Nash, MS, PA

OTHER HIGH-YIELD POINTS

- Considered **carcinoma in situ**
- Asymptomatic, detected incidentally
- IHC: **p53** mutant staining pattern; **high Ki67**
- **Differential Diagnosis**:
  - **Secretory Cell Outgrowth (SCOUT)**: 30 or more tubal secretory cells in a linear stretch, with no intervening ciliated cells, wildtype p53 expression
  - **Serous tubal intraepithelial lesion (STIL)**: intermediate features
- **SEE-FIM** (Sectioning and Extensively Examining the Fimbriated End)
  - Grossing protocol developed for thorough assessment of fallopian tube precursor lesions in women with ovarian tumors

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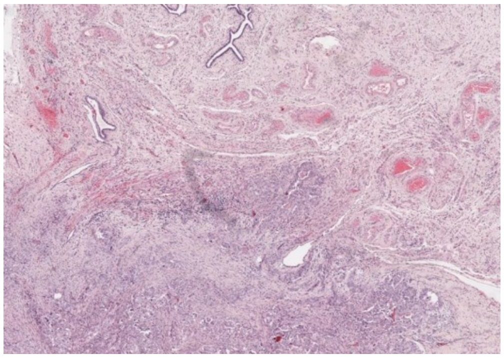
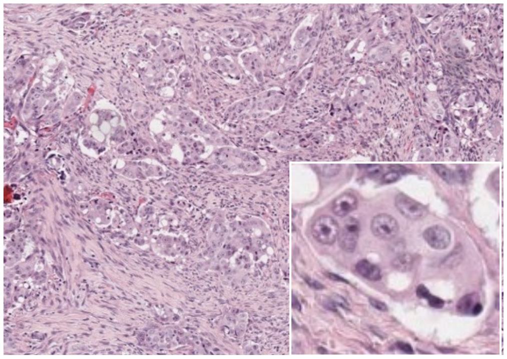


Invasive tumor in fallopian tube wall



Clusters of tumor cells with high-grade features (serous)

PRIMARY ADENOCARCINOMA OF FALLOPIAN TUBE

MORPHOLOGY

- Dilated fallopian tube lumen filled with yellow to tan nodules or mass
- Most are in the **distal 2/3rds**, minority located in the fimbriated end
- Histologic type is **serous in 80% of cases**; others include: endometrioid (7%), clear cell (2%), mucinous (2%), mixed serous-mucinous (1%) or NOS (10%)
- Serous carcinoma shows broad papillae, nests, or sheets of cells with high-grade nuclei (enlarged, hyperchromatic, irregular nuclear chromatin) with prominent nucleoli, irregular nuclear membranes and abundant mitoses

OTHER HIGH-YIELD POINTS

- Accounts for <1% of malignancies of the female genital tract
- Difficult to distinguish from ovarian serous carcinoma by morphology
- Primary serous carcinoma of the fallopian tube should show tubal epithelial transition from benign to malignant, and unremarkable ovaries

Differential diagnosis	Key feature(s)
Primary fallopian tube carcinoma	STIC present Tubal mass or tubo-ovarian mass
Primary ovarian carcinoma	No STIC Ovarian mass
Primary peritoneal carcinoma	No STIC Omental/peritoneal mass

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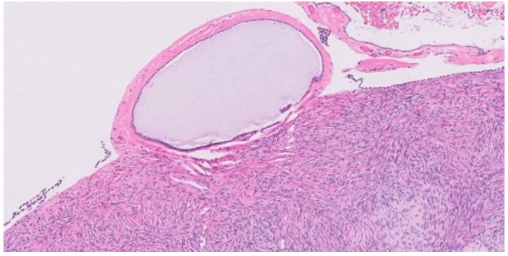
NON-NEOPLASTIC LESIONS OF THE OVARY

Thin-walled cysts lined by flattened epithelium



EPITHELIAL INCLUSION CYST

MORPHOLOGY

- Sometimes visible grossly, **always <1 cm in size (if > 1cm, cystadenoma)**
- **Lining epithelium** is variable: may be columnar, cuboidal, flattened, ciliated or may show apocrine metaplasia
- Diagnostic pitfalls:
  - Sometimes, epithelial inclusion glands and cysts may show vacuolation/clearing and displacement of nuclei to the periphery by the cytoplasmic vacuole, **mimicing signet ring cell carcinoma**
  - Additional sectioning demonstrates a relation to epithelial inclusion

- These **vacuolated cells are negative for mucin** (versus mucin positive signet ring cells)

OTHER HIGH YIELD POINTS

- Arise from invaginations of the surface epithelium that have lost connection with the surface
- Epithelial inclusion cysts are **precursors** of epithelial ovarian tumors

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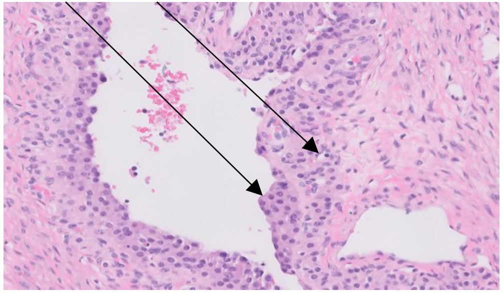
Granulosa and theca cells lining the cyst wall



Luteinized follicular cyst of the ovary

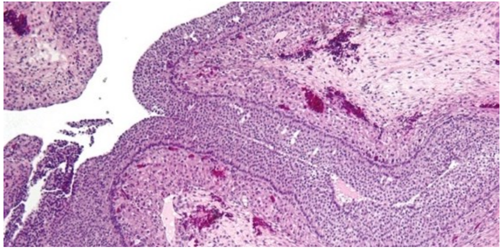


Image by Dr. Michael Bonert on Wikimedia

FOLLICLE CYST (FC)

MORPHOLOGY

- Lined by **layers of inner granulosa cells and outer theca cells**
- Cells in both layers are uniform with round to oval nuclei
- Can be distinguished from each other by a **reticulin stain** (dense reticulum surrounding theca cells, but absent in granulosa cells)
- **Large solitary luteinized follicle cyst of pregnancy and puerperium**: lining cells are luteinized with abundant eosinophilic cytoplasm with focal nuclear atypia

OTHER HIGH-YIELD POINTS

- Thin-walled cyst measuring ≥3 cm **versus *cystic follicle* that measures <3 cm**
- Commonly seen in **non-pregnant women of reproductive age**, usually around menarche or menopause
- Associated syndromes:
    - **McCune Albright Syndrome**: solitary or multiple FCs
    - **Cystic fibrosis**: predisposition to develop solitary FCs in post-pubertal women with cystic fibrosis

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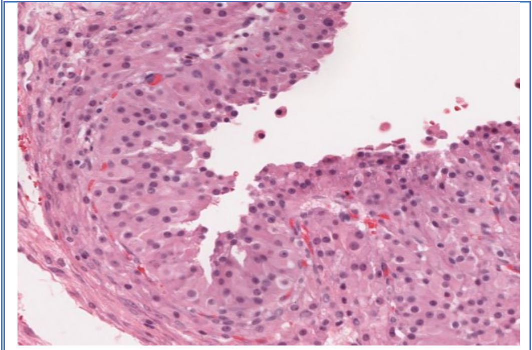
HYPERREACTIO LUTEINALIS

MORPHOLOGY

- Gross: multiple, thin-walled, small cysts causing **moderate to massive ovarian enlargement**
- **Prominent luteinization** of theca interna cells, sometimes granulosa cells
- Granulosa cells may show **bizarre nuclei**

OTHER HIGH YIELD POINTS

- **Bilateral** ovarian enlargement due to **multiple follicle cysts** resulting from **hCG** stimulation
- Show **spontaneous regression** after puerperium
- When associated with **trophoblastic** disease, show regression after evacuation of molar disease



Large inner granulosa cells, small outer theca cells

CORPUS LUTEUM CYST

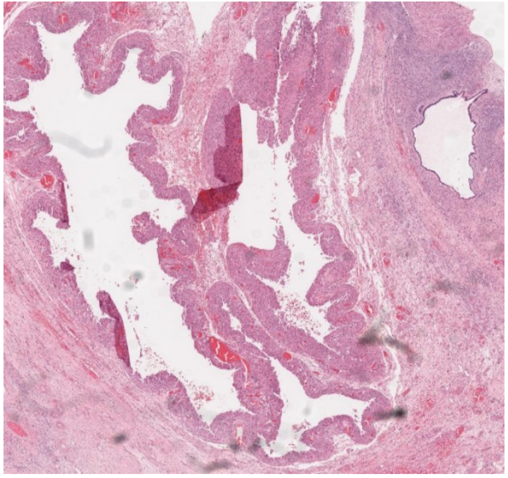
MORPHOLOGY

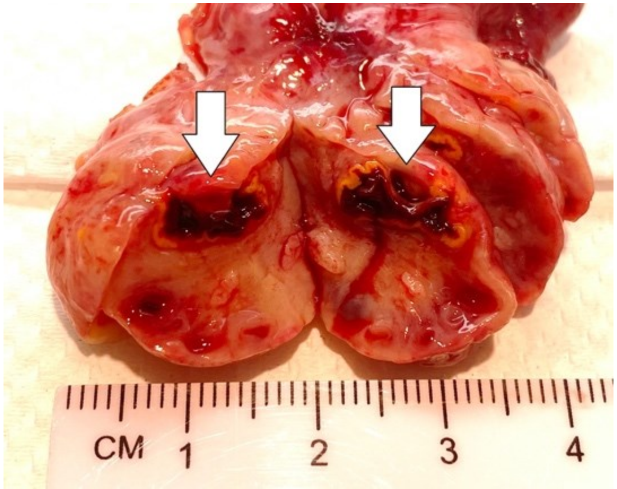
- Gross: convoluted, yellow lining with serous, serosanguinous or clotted blood contents
- **Convoluted lining** composed of large inner luteinized granulosa cells with small outer theca interna cells

OTHER HIGH YIELD POINTS

- Usually occur during **reproductive age**; rarely, can be seen in neonates or in postmenopausal women following sporadic ovulation
- Found in 10-15% of pelvic lymph node dissections and omenctectomies
- Associated with inflammatory tubal disease and epithelial ovarian tumors
- Origin: secondary mullerian system or dislodged fimbrial cells
- Clinical features: asymptomatic, **incidental finding**

Convoluted cyst lining





Corpus luteum cyst with bleeding (photo courtesy of Mikael Haggstrom MD)

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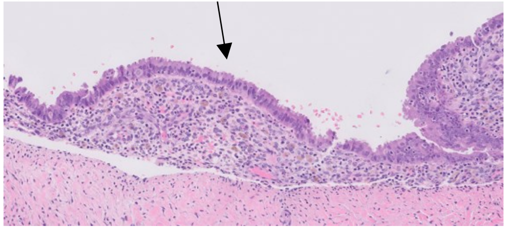
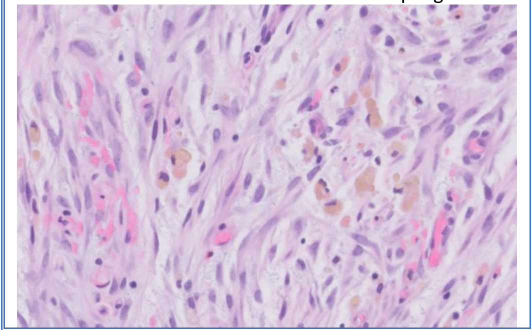
Cyst wall lined by endometrial epithelial lining



Endometrial stroma and hemosiderin macrophages



ENDOMETRIOTIC CYST

MORPHOLOGY

- Gross: cyst with fibrotic walls, smooth lining, and brown contents (partly digested/hemolyzed blood) – "**chocolate cyst**"
- Must satisfy criteria for endometriosis - i.e., **two of following three criteria:**
  - Endometriotic glands
  - Endometrial type stroma
  - Evidence of chronic hemorrhage (e.g., hemosiderin-laden macrophages)

OTHER HIGH YIELD POINTS

- **Cystic form** of endometriosis: **ectopic endometriotic tissue** forming a cyst-like structure with bloody contents
- Carcinomas that **most commonly** arise from endometriotic cysts: **endometrioid carcinoma, clear cell carcinoma**
- Atypical endometriosis: lining epithelium of the endometriotic cyst shows **cytologic atypia**, precursor lesion to carcinoma
- Most common mutation seen in endometriotic carcinoma arising from: **ARID1A (**other mutations include: PTEN, PIK3CA, KRAS)

Path Presenter

OVARIAN TORSION

MORPHOLOGY

- Gross: swollen fallopian tube and edematous ovary with dusky discoloration
- **Ischemic necrosis** of the ovarian tissue, any underlying pathology may also be seen

OTHER HIGH YIELD POINTS

- Torsion is usually a complication of underlying pathology: usually cyst, abscess, or tumor (rarely occurs in normal ovaries)
- Clinical findings are similar to acute appendicitis
- Torsion i.e. **twisting of fallopian tube** cuts off the blood supply to the ovary resulting in infarction of ovary

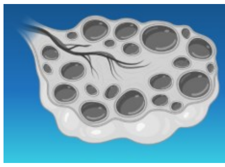
STREAK OVARIES

MORPHOLOGY

- Gross: thin, fibrotic appearing streak-like gonadal tissue
- **Fibrous tissue only**, lacking any ovarian stroma or follicles

OTHER HIGH YIELD POINTS

- Streak ovaries (gonadal aplasia, hormonal failure) are seen in congenital or acquired gonadal agenesis or dysgenesis disorders
- Congenital disorders include karyotypic abnormalities such as 46XX, 46XY or 45XO (**Turner syndrome**)
- Acquired causes of streak ovaries: premature ovarian failure, premature follicular depletion (various underlying causes)
- Tumors can arise in streak ovaries/streak gonads (e.g., **gonadoblastoma)**



15. GYNECOLOGIC PATHOLOGY

POLYCYSTIC OVARIAN SYNDROME (PCOS)

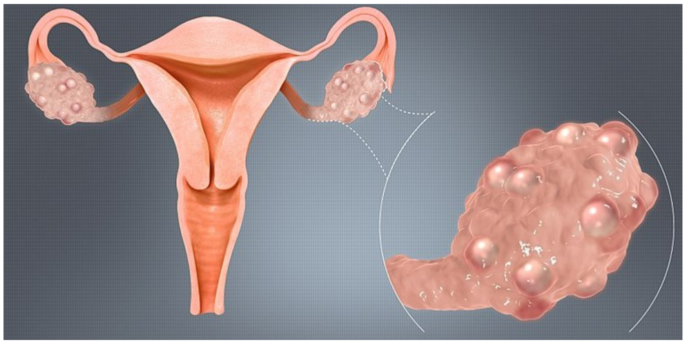


Photo courtesy of Scientific Animations (Wikimedia)

MORPHOLOGY

- Gross: 2-5x enlarged ovaries, unilateral or bilateral with smooth, lobulated surface due to multiple underlying cortical cysts; cut surface shows multiple cysts < 1 cm
- Cysts are seen in the outer cortical zone
- Cyst lining is atrophic usually – **atretic cystic follicles**
- May be accompanied by stromal hyperthecosis

OTHER HIGH YIELD POINTS

- Characterized by inappropriate gonadotropin secretion, chronic anovulation, hyperandrogenism, and increased peripheral conversion of androgens to estrogens, sclerotic ovaries, abnormal glucose tolerance and hyperinsulinemia
- **Defined ultrasonographically** by the presence of ≥12 follicles measuring 2-9 mm OR ovarian volume >10 cm^3
- Clinically, Rotterdam criteria used for diagnosis – **two of three** characteristics:
  - 1) Oligo-ovulation or anovulation
  - 2) Clinical and/or biochemical evidence of hyperandrogenism
  - 3) Polycystic ovary morphology on ultrasound with exclusion of other disorders

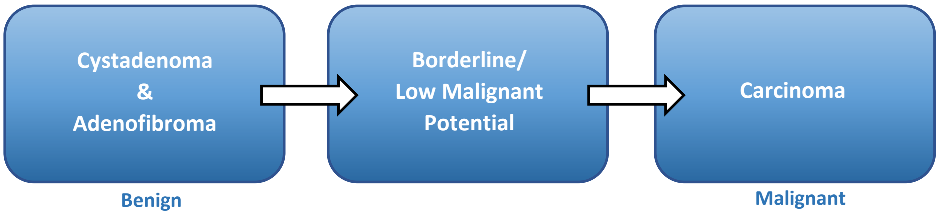
OVARIAN NEOPLASMS

BACKGROUND AND CLASSIFICATION

- Ovarian carcinomas are divided into two types:

	TYPE I	TYPE II
Entities	Low-grade serous carcinoma Mucinous carcinoma Clear cell carcinoma Endometrioid carcinoma	High-grade serous carcinoma High-grade endometrioid carcinoma Undifferentiated carcinoma Carcinosarcoma Transitional cell carcinoma
Molecular alterations	KRAS, BRAF, PIK3CA, MSI, HER2, PTEN, ARID1A	BRCA1, BRCA2, p53, HER2, AKT
Pathogenesis	Ovarian surface EIC → Precursor lesions (e.g., cystadenoma, adenofibroma) → **Type I malignancies**	Fallopian tubal origin → Precursor lesions (e.g., STIC) → **Type II malignancies**
Growth	Grow slowly	Grow aggressively

- Three levels of biologic potential



Cystadenoma & Adenofibroma → Borderline/ Low Malignant Potential → Carcinoma

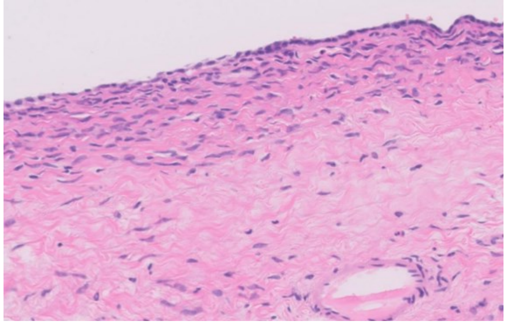
Benign

Malignant

	Serous	Mucinous	Endometrioid	Clear Cell	Brenner/ Transitional	Seromucinous
Benign	50%	80%	5%	<1%	99%	<1%
Borderline	15%	15%	20%	<1%	<1%	99%
Carcinoma	35%	5%	75%	99%	<1%	No longer an entity as of WHO 2020

- Seromucinous histologically exists, **but** likely not a true histomolecular entity that will eventually disappear as **likely composed of serous and endometrioid tumors**
- **Common mixtures** of epithelial tumors:
  - Brenner + mucinous cystadenoma or borderline
  - Serous + seromucinous borderline
  - Endometrioid + clear cell carcinoma

Cuboidal to flattened epithelial lining



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SEROUS CYSTADENOMA/ADENOFIBROMA

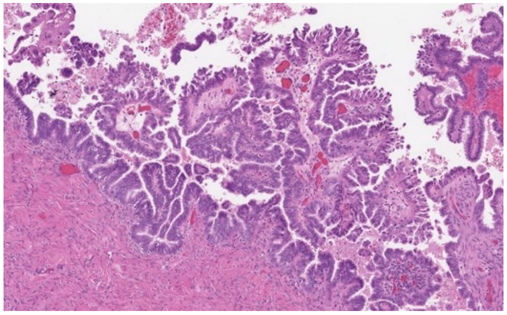
MORPHOLOGY

- **Variably sized** but **>1 cm** by definition (**otherwise called cortical inclusion cysts**), cystic, with smooth outer and inner surface & filled with watery fluid
- **Cystadenomas predominantly solid** and punctuated with cysts and lined by non-stratified cuboidal or columnar cells
- **Adenofibromas** show small glands and cysts in a fibrous stroma
- If there are focal epithelial proliferations <10% tumor volume, the tumor is designated as cystadenoma with focal epithelial proliferation

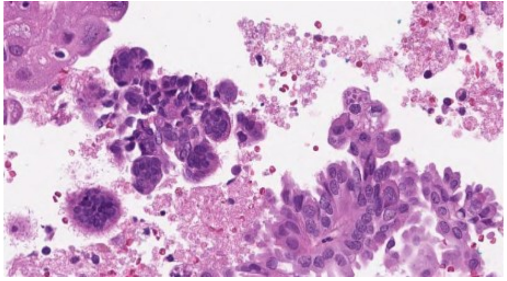
OTHER HIGH YIELD POINTS

- **Benign** but can recur after excision
- Wide age range: no specific age group
- Detected incidentally or present with a mass
- Stromal fibrous cells and epithelial cells can show DNA copy number changes

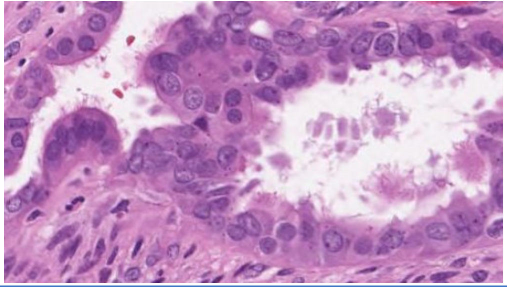
Hierarchical / tree branch-like architecture



Tufting and detachment of cells



Ciliated, uniform cells with high N:C ratio



SEROUS BORDERLINE TUMOR (SBT) OF OVARY

MORPHOLOGY

- Predominantly cystic, usually >5 cm, **showing excrescences or papillary growths** on the inner or outer surface of the ovary
- Cyst epithelium with **hierarchical (tree branch-like) branching papillae**, accounting for >10% of tumor volume, without any stromal invasion (**up to 5 mm of stroma invasion** is allowed in the **microinvasive type**)
  - Epithelium can show tufting and cell detachment
  - Budding clusters, free-floating clusters, free-floating single cells
  - **High N:C ratio**, small and uniform nuclei with small nucleoli; infrequent mitoses
  - Nuclear features should **NOT** be high-grade
- **Micropapillary/cribriform subtype**
  - Elongated micropapillae at least five times longer than they are wide, lacking stromal cores that directly emanate from large papillae
  - "Medusa-head" appearance
- **Stromal microinvasion (called "SBT with microinvasion")**
  - Defined as **invasion <5 mm** in any single focus
  - **No desmoplasia** should be present
  - If invasion is <5 mm, but morphology suggestive of low-grade serous carcinoma (LGSC), best classified as "**LGSC with microinvasion"**
- **Implant**
  - Extra-ovarian disease in the presence of SBT of ovary
  - **Non-invasive**, by definition
  - Presence of invasion → **extra-ovarian LGSCs**
  - Non-invasive implants can be **epithelial or desmoplastic**
  - **Epithelial implants** show hierarchically branching papillae or detached clusters of cells not associated with stroma
  - **Desmoplastic implants** show single cells or clusters of cells embedded in a reactive appearing stroma
  - When present on the ovarian surface → **autoimplants**

OTHER HIGH YIELD POINTS

SBT with micropapillary features

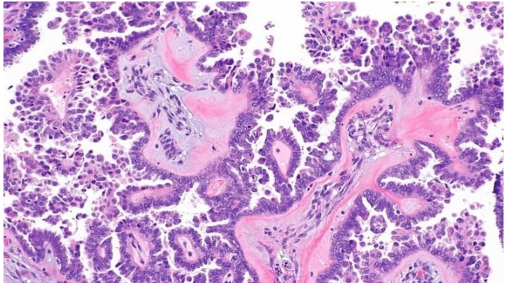


Image courtesy: Michael Bonert (Wikimedia)

- Median age of presentation is 50 years
- Usually presents with a mass; 1/3 of tumors are bilateral
- SBTs show mutations in **KRAS** or **BRAF**
- 4-7% of women with SBT develop subsequent carcinoma, mostly of low-grade type
- **Risk factors** associated with development of **invasive carcinoma**:
    - Bilateral tumors
    - Micropapillary/cribriform subtype
    - Ovarian surface involvement
    - Residual disease after surgery

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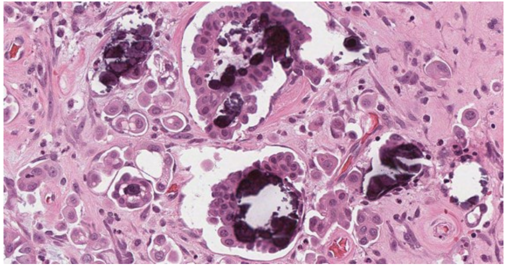
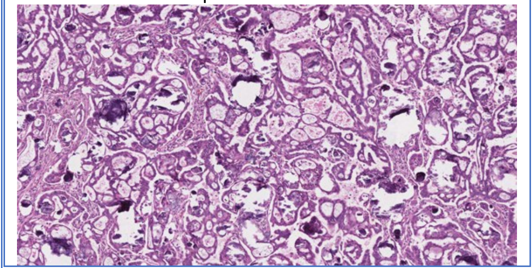
Mild to moderate atypia, calcifications



LGSC with numerous psammoma bodies



LOW-GRADE SEROUS CARCINOMA (LGSC)

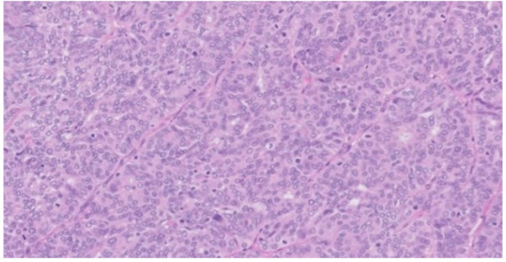
MORPHOLOGY

- Usually **bilateral**, exhibiting **papillary** growth
- **Calcifications/psammoma bodies** may be present, sometimes obscuring the carcninoma (**psammomacarcinoma**)
- Several patterns of invasion can be seen within the same tumor: small nests, glands, papillae, micropapillae, and inverted macropapillae
- Tumor cell nuclei show **mild to moderate atypia** with <3-fold variation in nuclear size
- Mitoses are present, but low: 3-5/10 HPF

OTHER HIGH YIELD POINTS

- Patients are about **a decade younger** than high grade serous carcinomas
- Significant proportion of LGSCs arise in association with SBT
- IHC: (+) ER, PR, PAX8, WT-1; p53 wildtype; p16 non-diffuse
- Molecular: KRAS, NRAS, BRAF, USP9X, and EIF1AX, loss of 9p, homozygous deletion of *CDKN2A/2B*.
    - **BRAF** mutation associated with high-stage tumors
    - **KRAS** mutation associated with tumor recurrence
- Indolent clinical course

High-grade serous carcinoma with solid architecture

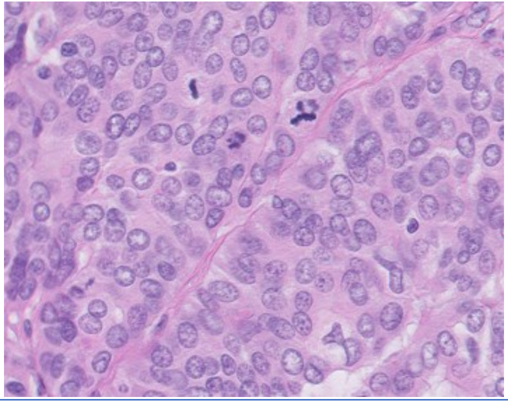


HIGH-GRADE SEROUS CARCINOMA (HGSC)

MORPHOLOGY

- Usually bilateral, large and exophytic
- Solid, papillary, glandular architecture, or slit-like spaces
- Nuclear **pleomorphism** (>3-fold variation in nuclear size)
- Numerous **mitoses** (>12/10 HPF)
- **Necrosis** is very frequent
- BRCA-related cancers often have **Solid, pseudo-Endometrioid, Transitional morphology** (“SET”) and lots of tumor-infiltrating lymphocytes

Pleomorphism, brisk mitoses

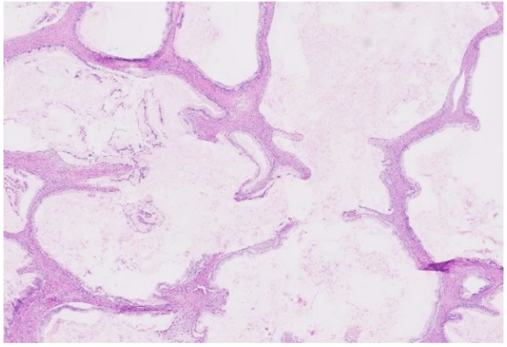


OTHER HIGH YIELD POINTS

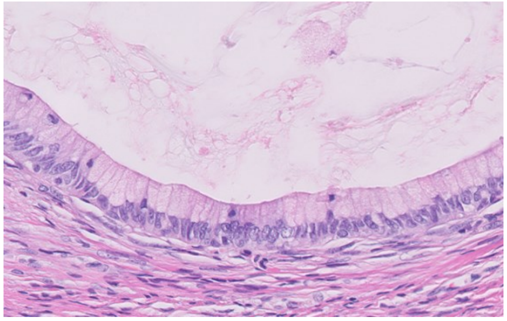
- **Most common ovarian carcinoma** (70% of all ovarian carcinomas), with higher incidence in white populations
- **BRCA1/2** → very high risk → often get prophylactic salpingo-oophorectomy (entirely submitted for histologic evaluation, especially fimbriae)
- Pathogenesis: arise from **tubal type epithelium**, as described above in **type II** ovarian carcinomas
- **TP53 mutations** most common
- ~15% cases show germline BRCA1/2 mutations
- Other less common mutations include: RAD51 C/D, BRIP1, or BRCA methylation

Path Presenter

Multiloculated cyst, abundant mucin



Mullerian type mucinous epithelium



MUCINOUS CYSTADENOMA/ADENOFIBROMA

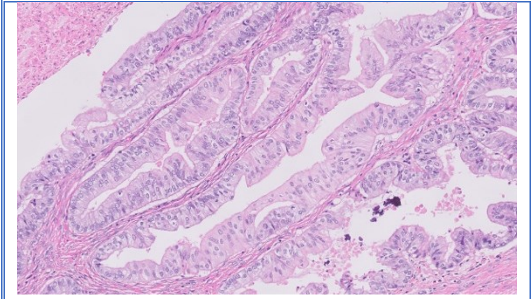
MORPHOLOGY

- Usually unilateral and multilocular with smooth surface
  - **Adenofibromas** are smaller, mostly **solid** punctuated with smaller cysts
- Cysts lined by **mucinous epithelium**
- Mucinous epithelium can be of **3 different types**:
  - **Mullerian** type
  - **Gastric** foveolar type
  - **Intestinal** type with goblet cells sometimes with neuroendocrine and Paneth cells
- Adenofibroma has mainly **fibrous** stroma
- Nuclei are small, basally located, **no atypia**, minimal mitoses
- Focal **mucin extravasation** may be present, leading to mucinous granulomas (does NOT mean invasion)

OTHER HIGH YIELD POINTS

- **Benign**, occur over a wide age range (median age of **50 years**)
- Commonly associated with other tumors: Brenner tumor and dermoid cyst, less commonly with mural nodules of borderline tumor, clear cell carcinoma, large cell neuroendocrine, and sex cord stromal tumor
- *KRAS* mutations **very common**
- Benign, prone to recurrences due to mucin spillage during removal

Path Presenter

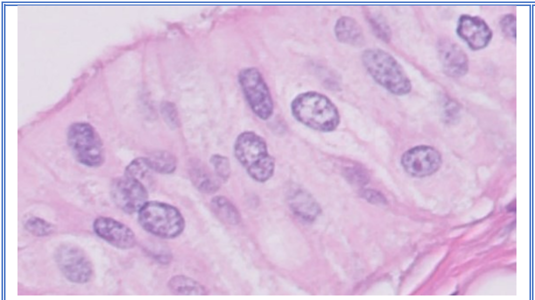


Architecturally complex

MUCINOUS BORDERLINE TUMOR (MBT)

MORPHOLOGY

- **Large, almost always unilateral**
- Smooth surface, multiloculated, with some solid areas
- Grossing recommendation:
  - For tumors <10 cm – 1 section per cm
  - For tumors ≥10 cm – 2 sections per cm
- Architecturally **complex, non-invasive** tumors
- **Epithelium is always of gastrointestinal type**, but shows tufting, stratification and papillae; **low-grade atypia**
- Mitoses seen mainly in crypts
- **Intraepithelial carcinoma**: areas with marked atypia with increased mitoses



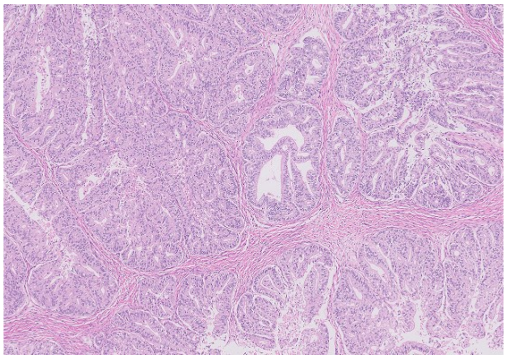
Multilayered mucinous epithelium

- **Microinvasion**: single cells or small groups of cells **measuring <5 mm in greatest dimension** invading into the stroma with same degree of atypia as borderline tumors

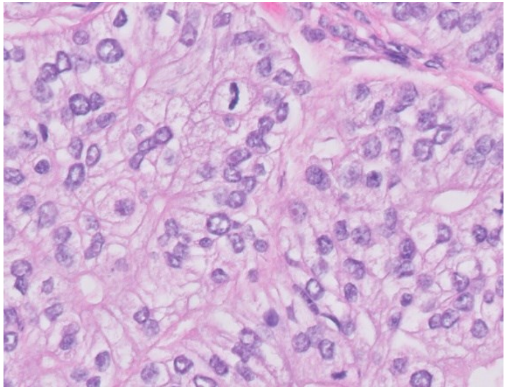
OTHER HIGH YIELD POINTS

- *KRAS* mutations in 30-75% tumors; *P53* mutations less common than in carcinomas
- Prognosis is generally **very good**, even with intraepithelial carcinoma

Path Presenter



Expansile/confluent pattern of invasion



Nuclear atypia with prominent nucleoli and brisk mitoses

Path Presenter

MUCINOUS CARCINOMA

MORPHOLOGY

- Typically large, unilateral, solid and cystic
- **Invasive** mucinous neoplasm with **gastrointestinal-type epithelium** and **nuclear atypia** ranging from mild to severe
- Invasion is of two types:
  - **Expansile/confluent pattern**: (more common) marked glandular crowding with little or no stroma in between (labyrinthine pattern)
  - **Infiltrative/destructive pattern**: irregular glands and nests; single cells in a desmoplastic stroma should raise suspicion for metastasis

OTHER HIGH YIELD POINTS

- Most arise from **MBT**, some from **mature cystic teratoma** or **Brenner** tumor
- IHC: (+) CK7, CK20, CEA, CDX-2, CA19-9; (-) CA125, WT1, NapsinA, ER, PR
- Diffuse strong reactivity for **SATB2** is seen in mucinous carcinomas associated with **mature teratomas**
- Most common mutations include CDKN2A, KRAS and TP53
- *ERBB2* amplifications in 1/4, always with concurrent *TP53* mutation
- Usually good prognosis; poor in advanced stages
- Very important to distinguish primary ovarian tumors from metastasis:

	Primary Ovarian	Metastasis
Laterality	Unilateral	Bilateral
Size	Large (usually >20 cm)	Smaller (usually <10 cm)
Gross	Multicystic + solid component	Nodule with cystic component
Location within ovary	Within stroma	Surface and stroma
Microscopic	Usually confluent pattern of invasion	Almost always infiltrative pattern
Extraovarian disease	Usually absent	Often present

OVARIAN MUCINOUS TUMOR IMMUNOHISTOCHEMISTRY

	CK7	CK20	ER/PR	CDX2	SATB2	PAX8
Ovarian mucinous borderline and carcinoma	+	-/+	-	+	-	+/-
Ovarian seromucinous borderline and carcinoma	+	-	+	-	-	+
Metastatic Colon Cancer	-/+	+	-	+	+	-
Metastatic Gastric Cancer	+	-/+	-	+	-	-
Metastatic low-grade appendiceal mucinous neoplasm (LAMN)	-/+	+	-	+	+	-

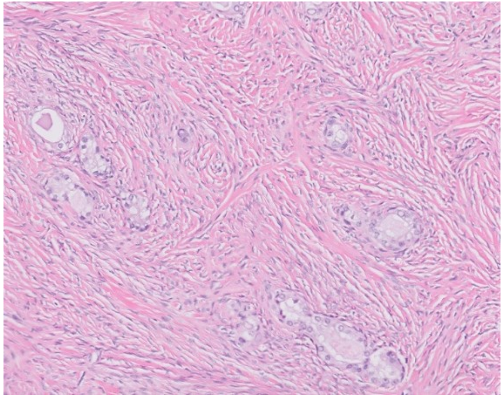
- Likely best panel:
  - **CK7** (strong positive in **ovarian**)
  - **SATB2** (strong positive in **lower GI)**
  - **PAX8** is helpful if positive but is not always positive in primary ovarian (*specific, but not sensitive)*

OVARIAN MUCINOUS BORDERLINE TUMOR VERSUS LOW-GRADE APPENDICEAL MUCINOUS NEOPLASM

	Primary Ovarian Mucinous Borderline Tumor	Secondary involvement by a Low-Grade Appendiceal Mucinous Neoplasm (LAMN)
Size	Large (>20 cm)	Variable (usually <20 cm)
Laterality	Unilateral	Bilateral
Location of tumor	Within stroma, rarely on surface	Surface and stromal involvement
Pseudomyxoma ovarii	Usually absent	Prominent
Amount and pattern of epithelium	Abundant; organized cysts	Scant; haphazard
Appendiceal tumor	Absent	Present

Adapted from a presentation by Dr. Anne Folkins, Stanford University

Benign, round glands embedded in fibromatous stroma



CLEAR CELL CYSTADENOMA/ADENOFIBROMA

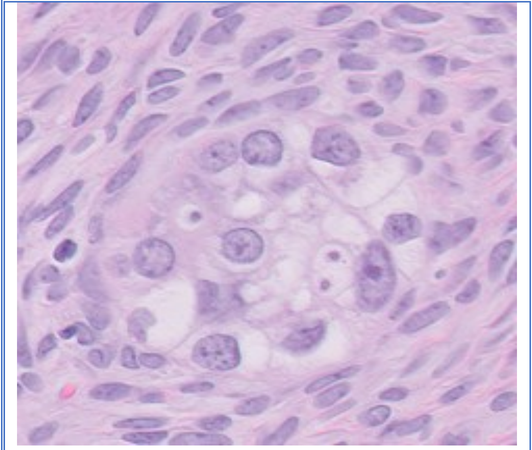
MORPHOLOGY

- Small to medium sized benign-appearing glands in a fibromatous stroma
- Cells are cuboidal or flat with clear, eosinophilic, or oxyphilic cytoplasm (doesn't have to be clear cytoplasm!)
- By definition, **NO papillae, crowding atypia or desmoplasia**
- Adenofibromas appear grossly as solid, firm growth

OTHER HIGH YIELD POINTS

- Median age 6th decade
- **Benign, very rare** (incidence unknown), almost always unilateral
- Can arise in association with **endometriosis**

Path Presenter



Clear cells, prominent nucleoli

CLEAR CELL BORDERLINE TUMOR

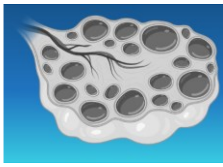
MORPHOLOGY

- Variably sized glands in a fibromatous stroma
- Cells are cuboidal or flat with clear to eosinophilic cytoplasm
- Nuclei are enlarged, sometimes with prominent nucleoli
- **Glands are irregular and crowded** with only minimal nuclear stratification
- **By definition, dense aggregates, papillary or tubulocystic architecture are absent** (if present, consider clear cell carcinoma)

OTHER HIGH YIELD POINTS

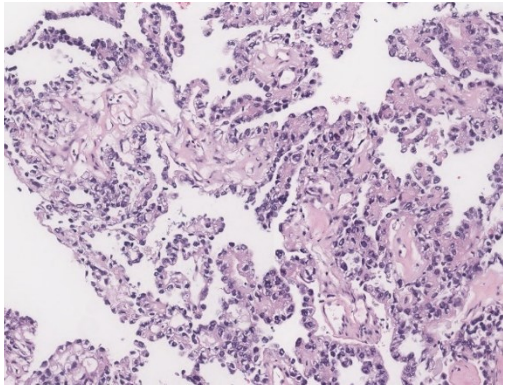
- **Rarely found in isolation**, almost always seen as a component of clear cell carcinoma; can arise in association with **endometriosis**
- ***PIK3CA*** and ***ARID1A*** abnormalities
- Usually **unilateral, good prognosis**, no known recurrence

Path Presenter

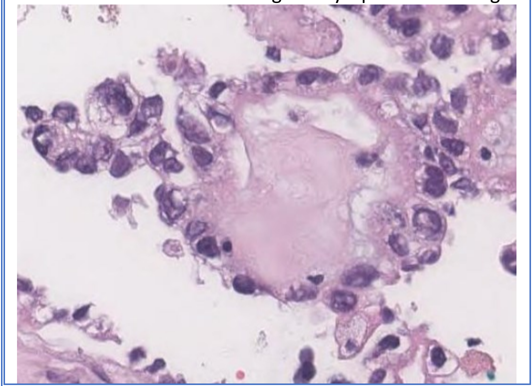


15. GYNECOLOGIC PATHOLOGY

Papillary architecture



Cuboidal cells with hob-nailing and cytoplasmic clearing



CLEAR CELL CARCINOMA

MORPHOLOGY

- When seen in association with endometriosis, seen grossly as **yellow nodules** protruding into a cyst
- Variable architecture including components of papillary, tubulocystic, and/or solid
- Cells are hobnail, cuboidal or flattened – **deceptively bland looking!**
- Cytoplasm varies from clear to eosinophilic
- Some can be **signet ring cells** or **targetoid cells**
- Nuclei are large and hyperchromatic with prominent nucleoli
- Cells are arranged in a single layer with **minimal stratification**
- Other features include stromal hyalinization, myxoid stroma, hyaline bodies, psammoma bodies

OTHER HIGH YIELD POINTS

- Mean age of 56 years, usually **unilateral**
- **Endometriosis** is found in 50-74% patients
- IHC: (+) PAX8, NapsinA, HNF1β; (-) WT1, ER, PR
- Common mutations: ***ARID1A*** loss of function and ***PIK3CA***
- **Lynch syndrome (MMR deficiency)** is a predisposition
- ***HNF1B* expression lowers the risk** through epigenetic mechanisms
- Most common ovarian carcinoma to be associated with **paraneoplastic hypercalcemia** and **venous thromboembolism**
- Prognosis depends on stage

Path Presenter

ENDOMETRIOID CYSTADENOMA/ADENOFIBROMA

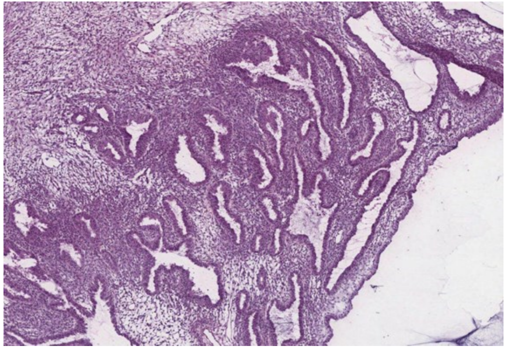
MORPHOLOGY

- Adenofibromas are solid with a **firm white surface**,
- May occur as **nodule in the cyst wall**
- Squamous morules, mucinous differentiation, and dystrophic stromal calcifications can occur
- Usually **unilocular cysts** lined by endometrioid epithelium *without* endometrial-type stroma (difference from endometriotic cyst / endometrioma!)

OTHER HIGH YIELD POINTS

- Benign, uncommon
- Likely represent endometrioma with indistinct endometrial stroma

Crowded irregular glands

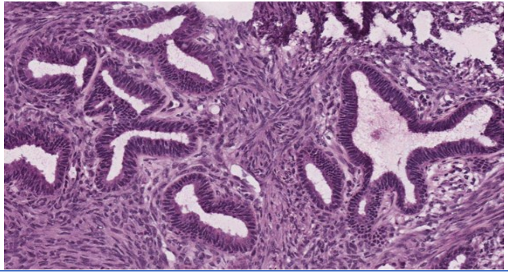


ENDOMETRIOID BORDERLINE TUMOR

MORPHOLOGY

- Usually **unilateral**, 3-10% are bilateral
- Two types of growth patterns: adenofibromatous & intracystic
- **Adenofibromatous:**
  - Component of **adenofibroma** seen in **~1/2** of tumors
  - Crowded, irregular glands with lobular architecture
  - Squamous and or mucinous metaplasia can occur
  - Nuclei show mild-moderate cytologic atypia with low mitotic activity
- **Intracystic:**
  - Papillary proliferation protruding into an endometrial cyst
- **Microinvasion***:* **<5 mm**
  - If >5 mm of confluent invasion or destructive invasion → **endometrial carcinoma**
- Can **resemble atypical hyperplasia/endometrial intraepithelial neoplasia (EIN)** when glands are back-to-back and cells with moderate atypia

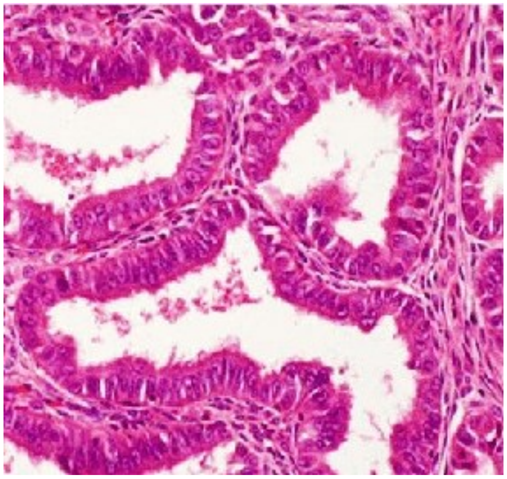
Mild to moderate cytologic atypia, irregular glands



OTHER HIGH YIELD POINTS

- **Rare tumor** with a mean age of 46-55 years
- Commonly seen with co-existing endometrial hyperplasia and/or endometrioid carcinoma
- Also associated with **endometriosis** and **endometrioid adenofibromas**
- If severe enough atypia → **Intraepithelial carcinoma**
- Prognosis is excellent - no reported malignant behavior

Well-differentiated endometrioid carcinoma



Courtesy Mikael Häggstöm, MD (Wikimedia)

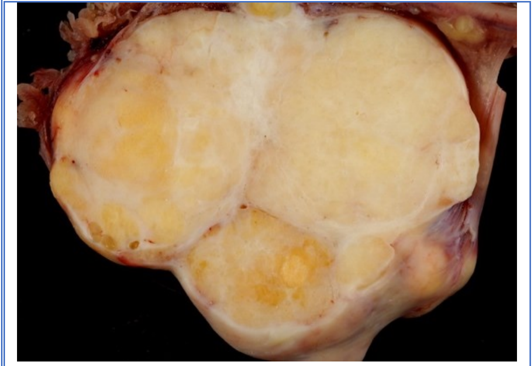
ENDOMETRIOID CARCINOMA OF THE OVARY

MORPHOLOGY

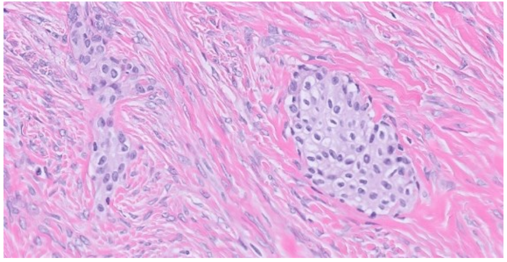
- Usually large and **unilateral**
- Solid and cystic cut surface with areas of hemorrhage and necrosis
- **Back-to-back glands with confluent or cribriform growth**
- Complex villoglandular, papillary, or Labyrinthine glands
- Less commonly destructive growth
- Squamous morules common; occasional mucinous metaplasia

OTHER HIGH YIELD POINTS

- Mean age is 55 years; strong association with **endometriosis** (85-90%)
- May occur in the setting of **Lynch syndrome (MMR deficiency)**
- **Protective factors**: early menopause, tubal ligation, high parity
- Increased risk if family history of breast cancer in first degree relative
- One fourth of patients have **concomitant endometrial hyperplasia and/or endometrioid endometrial carcinoma**
- Few cases arise from benign or borderline endometrioid adenofibromas
- Molecular: β-Catenin/Wnt pathway dysregulation, PTEN inactivation, PIK3CA, ARID1A, and **TP53 (in high-grade)**
- IHC: (+) ER/PR; (-) WT-1; **P53 can be positive in high-grade endometrioid**



Grey-white to yellow cut surface (Image courtesy of Ed Uthman, MD from Wiki images)



Oval to irregular nests of bland transitional epithelium

BRENNER TUMOR

MORPHOLOGY

- Most are small (<2 cm), rarely >10 cm
- Solid with a **grey-white to yellow cut surface** and a rubbery consistency
- Small, oval to irregular nests of **bland transitional/urothelial-type epithelium** embedded in a dense, fibrous stroma
- Cells are oval and show **characteristic nuclear grooves**
- There may be microcystic spaces, which are lined by transitional, mucinous, ciliated or cuboidal epithelium
- Calcifications can be focal or extensive

OTHER HIGH YIELD POINTS

- Wide age range, but commonly in the 5th to 7th decade
- May arise from **Walthard cell rest,** or from **germ cells in a teratoma**
- One-fourth associated with other tumors, usually mucinous tumors
- IHC: (+) GATA3, CK7, p63, S100P, AR, uroplakin, thrombomodulin
  (-) CK20, PAX8, ER, PR
- ***MYC* amplifications** can be seen
- **Benign** with no risk of recurrence or progression

Path Presenter

BORDERLINE BRENNER TUMOR

MORPHOLOGY

- Typically, large and cystic
- Can show papillary masses projecting into a cyst
- Rarely the tumor is completely cystic
- **Resemble low-grade papillary urothelial neoplasms of the urinary tract**
    - Uniform cells with round to oval nuclei and prominent nucleoli
- Mucinous or squamous metaplasia can be seen
- By definition, there is **NO stromal invasion**

OTHER HIGH YIELD POINTS

- Rare tumor, usually seen in patients >50 years of age
- IHC: (+) p63, GATA3; (-) WT1, ER and PR, p16; wildtype p53
- Mutations in *KRAS*, *PIK3CA* and *CDKN2A*

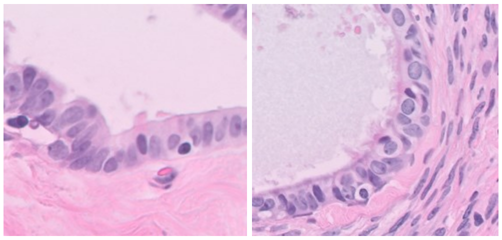
MALIGNANT BRENNER TUMOR

MORPHOLOGY

- Usually **large** (median size of 10 cm), may be solid or cystic with mural nodule
- Irregular, infiltrative masses of **highly atypical transitional / urothelial-type cells (resembles high-grade urothelial carcinoma)**
- Can show focal squamous differentiation
- **Desmoplastic stromal reaction is diagnostic of invasion**
- Need to demonstrate underlying Brenner tumor! Otherwise, likely serous carcinoma with transitional appearance or metastatic urothelial carcinoma

OTHER HIGH YIELD POINTS

- **<5% of Brenner tumors;** occur in women >50 years of age
- IHC: Focally (+) p16, (-) WT1, ER, PR; wildtype p53
- Mutations in *PIK3CA, MDM2*


Endometrioid (left) and ciliated (right) cyst linings

SEROMUCINOUS CYSTADENOMA/ADENOFIBROMA

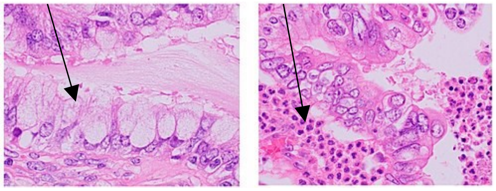
MORPHOLOGY

- Usually unilocular, sometimes multiloculated
    - Adenofibromas are solid with a dense fibrous cut surface or arise as nodules from the wall of an endometriotic cyst
- Hypocellular stroma with widely spaced glands lined by various Mullerian epithelium ciliated, endocervical type, mucinous, serous, and endometrioid

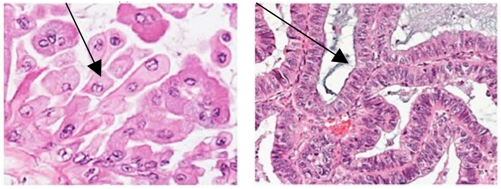
OTHER HIGH YIELD POINTS

- Very rare, benign; associated with endometriosis or endometriotic cyst

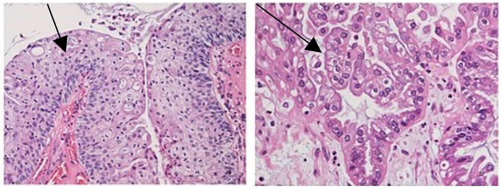
Mucinous cells; prominent neutrophilic inflammation



Indifferent cells, endometriotic epithelium



Squamous differentiation, clear cells with hobnailing



Images courtesy Michiko Nagamine & Yoshiki Mikami (Wikipedia)

Path Presenter

SEROMUCINOUS BORDERLINE TUMOR

MORPHOLOGY

- Smooth outer surface, unilocular cyst with friable papillary excrescences
- Solid areas are occasionally seen
- **Complex papillary growth**, edematous stroma, often abundant neutrophilic inflammation
- **Non-invasive**, proliferative epithelial tumor containing at least 2 types of epithelium:
    - Most often serous and endocervical-type mucinous
- Use term "**Müllerian Borderline Tumor**" if include endometrioid, clear cell, and/or transitional
- Lining cells are of varying types including endometrioid, endocervical, ciliated, hobnail type, clear cell type or indifferent

OTHER HIGH YIELD POINTS

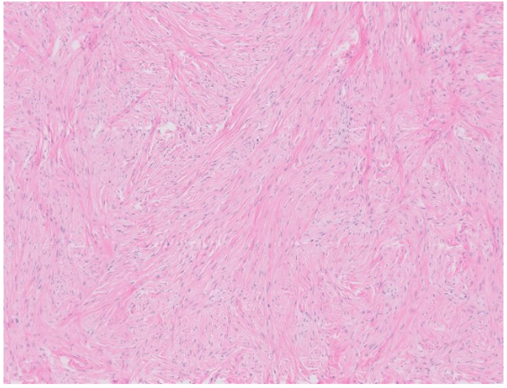
- **Uncommon** tumor, associated with endometriosis or endometriotic cyst
- Usually **younger** patients (~30s); 30% are bilateral
- Generally good prognosis, even with implants
- Show ***ARID1A*** mutations (loss of function)
- **Similarities with serous borderline tumor:** hierarchical and papillary growth, dissemination of peritoneal implants, can (rarely) progress to carcinoma
- **Differences from serous borderline tumor:** strong association with endometriosis, lower malignant potential, morphologically resembles endometrioid tumors with mucinous metaplasia, **little to absent WT-1 staining**, ARID1A mutations in many (like some endometrial)

SEROMUCINOUS CARCINOMA

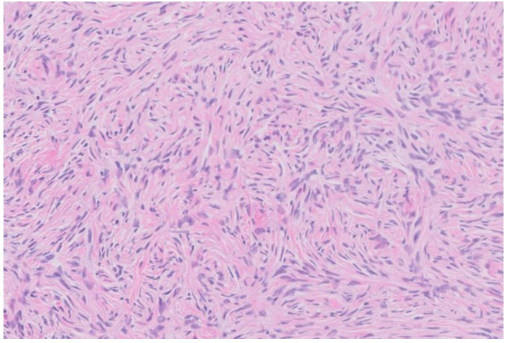
No longer a part of WHO 2020 – obsolete entity

OVARIAN SEX CORD STROMAL TUMORS

Intersecting fascicles in collagenized stroma



Bland spindle cells



FIBROMA

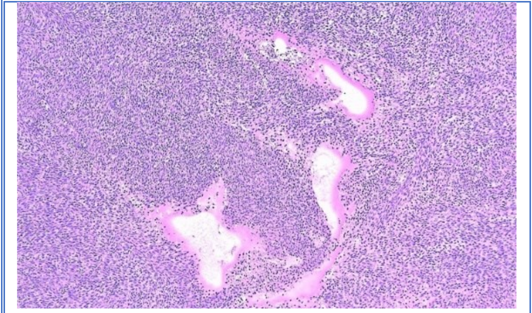
MORPHOLOGY

- Benign stromal tumor composed of fibroblastic cells
- Most are unilateral (occasionally bilateral) with smooth external capsule
- **Hard, chalky, white to yellow-white** cut surface
- More cellular tumors are tan and soft
- Focal areas of necrosis, hemorrhage and cystic degeneration can be seen
- **Intersecting fascicles** of spindled to ovoid cells with scant cytoplasm
- Stroma is variably **collagenized with hyaline plaques**
- Calcifications and (rarely) hyaline globules can also be seen
- **Cellular fibromas:** densely cellular with mild nuclear atypia, may show high mitotic activity
- Luteinized cells or a component of sex cord elements may be seen

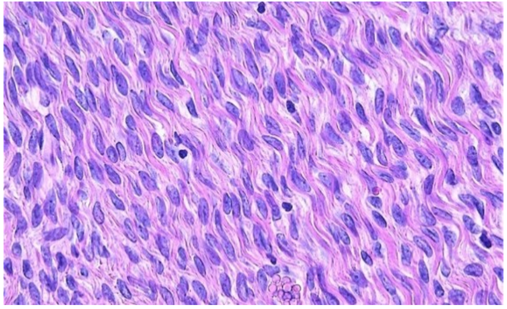
OTHER HIGH YIELD POINTS

- Mostly seen in **young patients**
- Associated with **nevoid basal cell carcinoma (Gorlin) syndrome**
- Also associated with **Meigs syndrome** (ascites and pleural effusion)
- Genetics: trisomy and/or tetrasomy 12, rarely *IDH1* mutation
- Cellular fibromas: loss of heterozygosity at 9q22.3(*PTCH1)* and 19p13.3(*STK11)*
- ***FOXL2* mutations are not seen** (seen in adult granulosa cell tumors)

Path Presenter



Thecoma with diffuse growth pattern



Pale grey cytoplasm and indistinct cell membrane
Images courtesy of @Patholwalker on Twitter

THECOMA

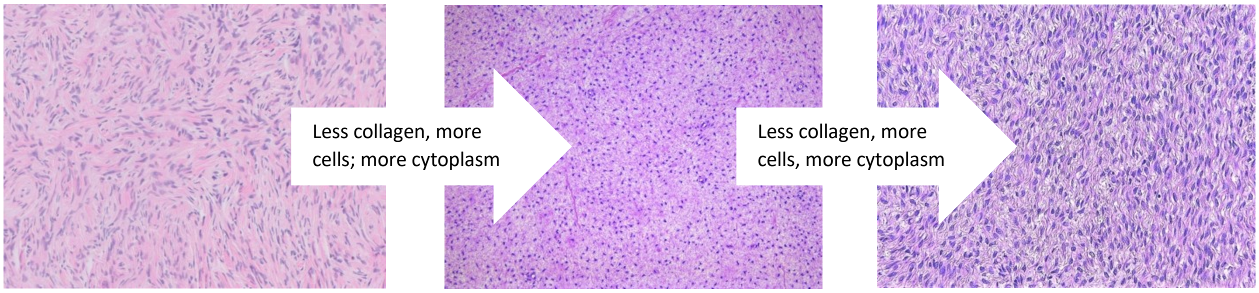
MORPHOLOGY

- Solid with **lobulated yellow-tan** cut surface
- Can show areas of necrosis, hemorrhage or cystic change
- Diffuse (less commonly, lobulated) growth pattern
- Cells are uniform with **pale gray cytoplasm and indistinct cell membrane**
- Rare cells are lipid rich
- Nuclei with prominent nucleoli, rarely with nuclear grooves
- Stroma usually scant with occasional hyaline plaques and keloid-like sclerosis
- Calcification and adipose metaplasia may be present
- **Reticulin** surrounds individual cells

OTHER HIGH YIELD POINTS

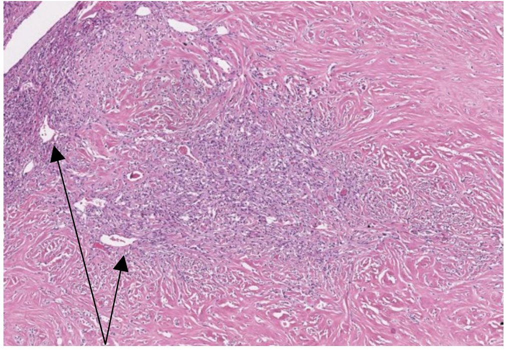
- Uncommon, typically in **postmenopausal women** (mean age 59 years)
- May present with hormonal manifestations: mostly estrogenic, less commonly androgenic
- Often associated with endometrial proliferative lesions
- Occasional cases can show *FOXL2* mutations

SPECTRUM OF FIBROMA, FIBROTHECOMA, AND THECOMA


Less collagen, more cells; more cytoplasm
Less collagen, more cells, more cytoplasm

Fibroma **Fibrothecoma** **Thecoma**

Cellular nodules separated by collagenous stroma



Thin, dilated blood vessels

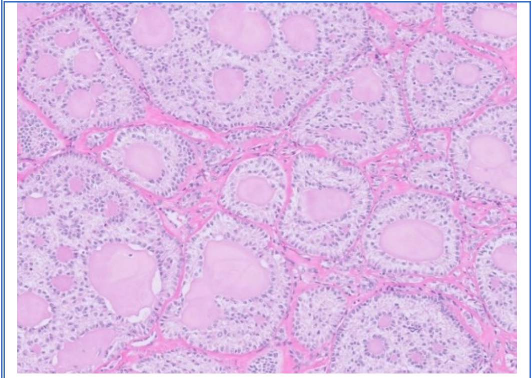
SCLEROSING STROMAL TUMOR

MORPHOLOGY

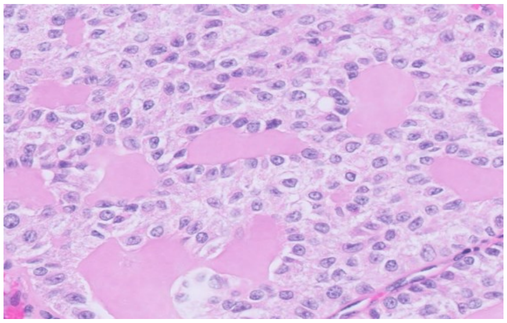
- Well-circumscribed with a **yellow to white** cut surface
- Central edema and cystic change can be seen
- Pseudo-lobular appearance with **cellular nodules** separated by edematous, collagenous, or occasionally myxoid stroma
- Cells are **spindled to epithelioid** with **clear to eosinophilic, vacuolated cytoplasm** (sometimes giving rise to a signet ring appearance)
- **Thin, dilated staghorn blood vessels**
- Can show prominent **luteinization during pregnancy**

OTHER HIGH YIELD POINTS

- Occurs in **young women** (mean age 29 years)
- Hormonal symptoms are uncommon but virilization and precocious puberty can be seen
- Molecular: *FHL2-GLI2* fusion genes or *GLI2* gene rearrangements



Rounded nests of cells with tubular architecture



Tall cells with pale cytoplasm and basal nuclei

SEX CORD TUMOR WITH ANNULAR TUBULES

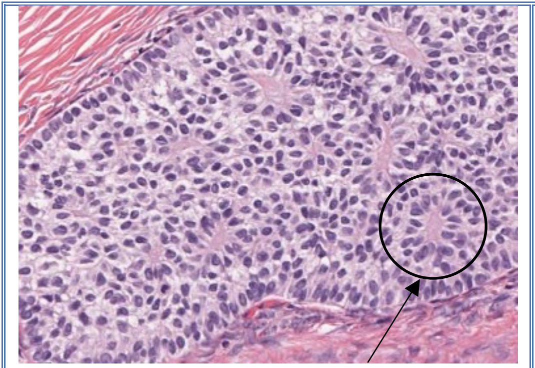
MORPHOLOGY

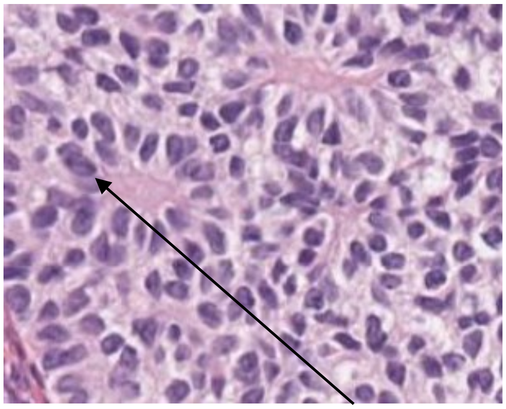
- **Solid and tan-yellow** cut surface
- Syndromic tumors may show a gritty texture
- **Cystic change** can be seen
- Rounded nests of **simple or complex tubules encircling hyaline basement membrane-like material**
- Cells are tall with pale cytoplasm and basal nuclei and antipodal arrangement of nuclei (at opposite ends)
- In Peutz-Jegher's syndrome:
  - ➢ Extensive calcification can be seen
  - ➢ Solid proliferation of sex cord cells or Sertoli-like tubular pattern can be seen
- Non-syndromic tumors can show cytologic atypia and mitotic activity

OTHER HIGH YIELD POINTS

- Can occur at any age
- Commonly seen in patients with **Peutz-Jegher's syndrome** (PJS, often incidentally discovered and bilateral/multifocal), benign clinical course
  - ➢ Germline mutations in ***STK11*** **gene** on chromosome 19p13.3
- **Non-syndromic** tumors usually unilateral and present with nonspecific symptoms including menstrual irregularities, sometimes progesterone-related symptoms; extra-ovarian spread in up to 20% of cases
- IHC: (+) calretinin, WT1, inhibin, SF1, FOXL2, CD56; (-) EMA, CD10

Path Presenter


Microfollicular architecture with Call-Exner bodies


Oval cells with elongated nuclei with nuclear grooves

ADULT GRANULOSA CELL TUMOR

MORPHOLOGY

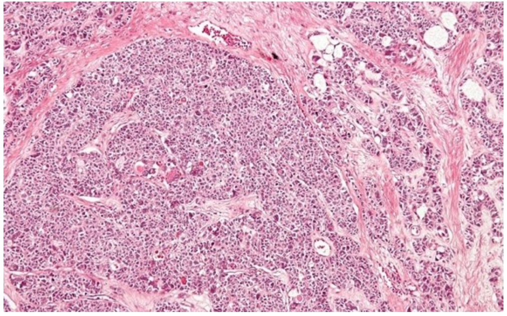
- May be solid and cystic or completely solid with a **soft, tan to yellow** cut surface, areas of hemorrhage are commonly seen
- Architectural **patterns**: diffuse, microfollicular (Call-Exner bodies), insular, macrofollicular, gyriform, watered silk, pseudopapillary
- Cells are round to oval with elongated nuclei with **irregular nuclear membranes and longitudinal grooves**
- Luteinization can occur
- May show **high-grade transformation** with cytologic atypia and mitoses

OTHER HIGH YIELD POINTS

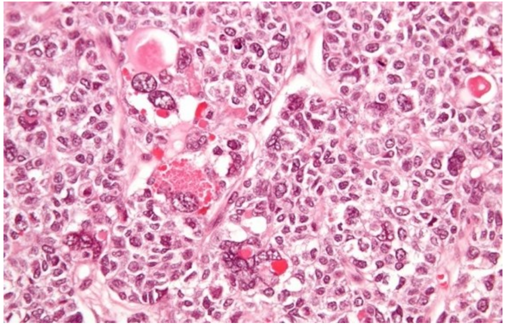
- Can occur at **any age**, but commonly seen in **perimenopausal** age group
- **Concurrent endometrial hyperplasia and/or endometrioid adenocarcinoma** can be seen (hormonal/estrogenic manifestations)
- **Androgenic manifestations** can be seen in 10% cases (more common in tumors with cystic changes)
- Hemoperitoneum can be seen in 10% cases
- May have **elevated serum β-inhibin levels**
- IHC: (+) FOXL2, calretinin, inhibin, SF1, ER, CK, CD99; Negative for EMA, PAX8 and CK7
- Stage I tumors have good prognosis but known to have **late recurrences**; high grade transformation associated with aggressive behavior
- Recurrent somatic **FOXL2** C134W missense mutation

Path Presenter

Nodular, pseudopapillary architecture



Round to oval cells with nuclei that lack grooves



Images adapted from Michael Bonert, MD (Wikimedia)

JUVENILE GRANULOSA CELL TUMOR

MORPHOLOGY

- **Unilateral** mass
- May be solid and cystic or predominantly cystic
- **Tan to yellow to white** cut surface
- Areas of hemorrhage are commonly seen
- **Nodular, diffuse or pseudopapillary architecture**
- Follicles are irregularly shaped and often contain basophilic secretions
- Cells are round to oval with nuclei that **lack grooves**

OTHER HIGH YIELD POINTS

- Mostly occur in the **first 3 decades of life** with a mean age of 13 years
- Can also occur in adults despite the name "juvenile"
- Can show hormonal manifestation, commonly estrogenic:
  - Precocious pseudo puberty
  - Menstrual disturbances
  - Androgenic manifestations
- IHC: (+) calretinin, inhibin, SF1, WT1, CD99, CD56, EMA
- Can express FOXL2, but **lack *FOXL2* mutations**
- Usually **excellent prognosis**
- Rupture associated with increased recurrence risk

Large epithelioid cells with abundant eosinophilic cytoplasm

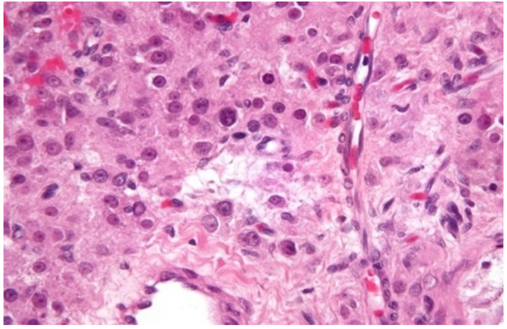


Image by Michael Bonert MD (Wikimedia)

LEYDIG CELL TUMOR

MORPHOLOGY

- Small, centered in **ovarian hilus** occsaional extension to ovarian stroma
- Well circumscribed; brown, red, or pink lobulated cut surface
- Nodular growth of round, large **epithelioid cells** with **abundant pale eosinophilic cytoplasm**
- Nuclei with single **prominent nucleoli**, occasional nuclear pseudo-inclusions
- **Reinke crystalloids** are quite specific but may not always be present
- Vessels may show fibrinoid change
- Uninvolved ovary may show hyperplasia of non-neoplastic Leydig cells

OTHER HIGH YIELD POINTS

- **Benign;** usually present with **endocrine manifestations**
- IHC: (+) calretinin, inhibin, melan-A

Cells in chords or trabeculae, cuboidal, bland oval-round nuclei, resemble immature seminiferous tubules

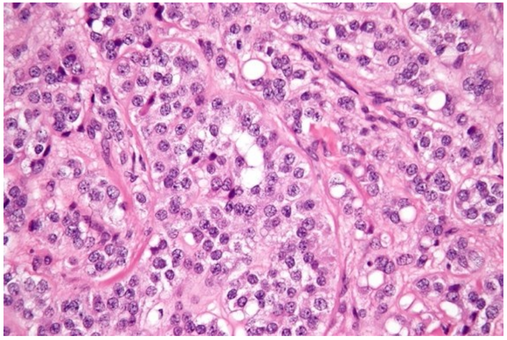


Image by Michael Bonert MD (Wikimedia)

SERTOLI CELL TUMOR

MORPHOLOGY

- **Solid with a tan-yellow** cut surface; ± hemorrhage and necrosis
- **Architectural patterns**: tubular, trabecular, diffuse, alveolar, pseudopapillary, retiform, and (rarely) pseudo-endometrioid, spindled
- Cuboidal or columnar with bland round nuclei and small nucleoli
- PJS associated tumors show lipid-rich and oxyphilic cells
- **Presence of occasional Leydig cells does not exclude the diagnosis of Sertoli cell tumor**
- **Features of malignant behavior**: tumor size > 5 cm, mitoses > $2/\text{mm}^2$, nuclear atypia and necrosis

OTHER HIGH YIELD POINTS

- Generally present with **estrogenic manifestations**
- **Some patients have Peutz-Jegher's syndrome**
- IHC: (+) Inhibin, SF1, calretinin, CD99, WT1, CK
  (-) EMA, CK7, PAX8, GATA3, Chromogranin
- Some tumors with ***DICER1*** mutations

Sertoli-Leydig cell tumor: solid-cystic, fleshy, pale yellow

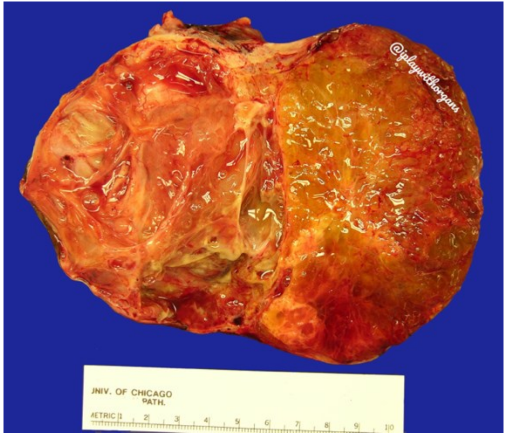


Image courtesy of Cory Nash, MS, PA(ASCP)

SERTOLI-LEYDIG CELL TUMOR (SLCT)

MORPHOLOGY

- Solid, solid-cystic or cystic; cut surface is **fleshy, pale yellow, pink or grey**
- Primitive gonadal stroma increases with increasing grade; the degree of tubular differentiation of the Sertoli cells component decreases with increasing grade
- **Well-differentiated SLCT:**
  - Almost always occur in **pure form**
  - Sertoli cells are arranged in open or closed tubules without nuclear atypia or mitotic activity
  - Leydig cells are present in cords, clusters or singly
- **Moderately differentiated SLCT:**
  - Have a **lobular** pattern of growth
  - Sertoli cells grow as nests, hollow or solid tubules, or cords
  - Cells show mild, moderate or rarely bizarre nuclear atypia
  - Mitotic activity is modest
  - Leydig cells are present as clusters at the periphery
- **Poorly differentiated SLCT:**
  - Abundant primitive gonadal stroma/sarcomatoid stroma
  - Minor component of moderately differentiated SLCT component
  - Conspicuous mitoses
  - **Leydig cells are sparse**

Sertoli cells grow as nests, tubules, or cords
Leydig cells present as clusters at periphery

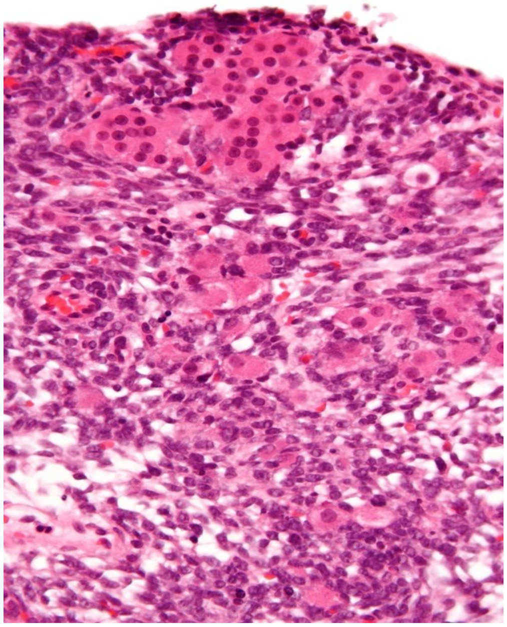
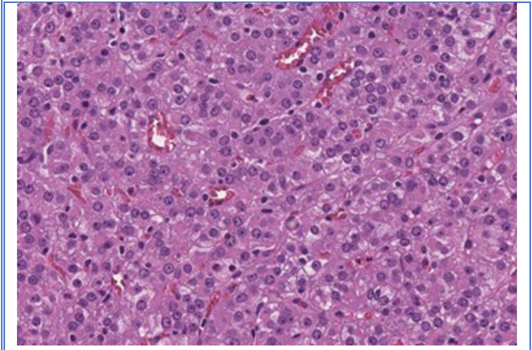


Image contributed by Michael Bonert, MD (Wikimedia)

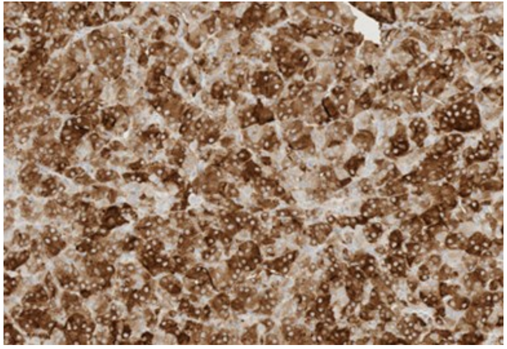
- **Retiform SLCT:**
  - Occur in **younger patients**
  - **Anastomosing, slit-like spaces, "sieve-like pattern" or papillae**
  - Small areas of retiform pattern may be seen in moderately differentiated or poorly differentiated tumors
  - Cells are **cuboidal or columnar**
- **Heterologous elements:**
  - Can be seen in moderately or poorly differentiated tumors
  - Include **epithelial elements** (most commonly benign enteric mucinous epithelium, less commonly borderline changes or carcinoma can be seen) OR **mesenchymal elements** consisting of cartilage or skeletal muscle can be seen in 20% tumors
  - **Carcinoid tumors** can occur rarely

OTHER HIGH YIELD POINTS

- IHC: (+) vimentin, CK, inhibin, calretinin, SF1, WT1, FOXL2
- Mostly sporadic but can occur in ***DICER1* syndrome**
- There are three molecular subtypes of SLCTs:
  - ***DICER1-mutant:*** younger patientsl moderately or poorly differentiated; retiform or heterologous elements
  - ***FOXL2* c.402C>G-*mutant:*** postmenopausal; moderately or poorly differentiated; no retiform or heterologous elements
  - ***DICER1/FOXL2*-wildtype*:*** indeterminate patient age; all well-differentiated tumors; no retiform or heterologous elements
- **Well-differentiated tumors have excellent prognosis**
- **Poor prognostic factors**: advanced stage, higher grade, retiform pattern, heterologous skeletal muscle, or cartilaginous differentiation



Large polygonal cells; (+) inhibin



STEROID CELL TUMOR

MORPHOLOGY

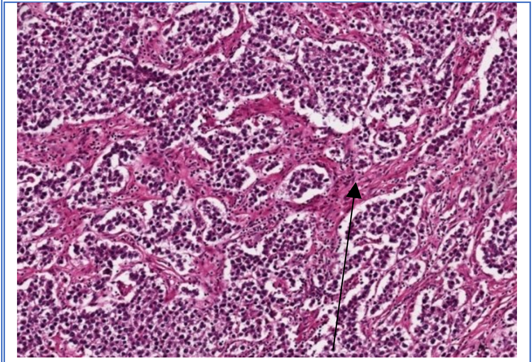
- **Solid, yellow, orange, red, brown, or black** cut surface
- Usually show a **diffuse growth pattern**, can also show nests, cords, pseudo-glandular or follicle-like arrangement of tumor cells
- Cells are **large, polygonal** with abundant eosinophilic (lipid-poor) to pale, vacuolated (lipid-rich) cytoplasm
- Intracytoplasmic lipochrome pigment may be seen; NO Reinke crystals
- Nuclei may be round with a prominent central nucleolus
- Can sometimes show stromal hyperthecosis

OTHER HIGH YIELD POINTS

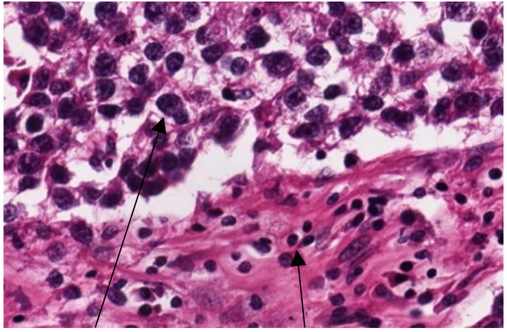
- Mean patient age is 43 years; can sometimes occur in **von Hippel-Lindau syndrome**
- **Androgenic manifestations** (50%) are more common than estrogenic manifestations
- Rarely progesterone effects or Cushing syndrome can be seen
- IHC: (+) inhibin, calretinin, melan A; **(-) FOXL2**
- One-third cases are malignant; predictors of malignant behavior:
  - Tumor size >7 cm
  - Increased mitotic activity
  - Significant nuclear atypia
  - Presence of necrosis, hemorrhage

15. GYNECOLOGIC PATHOLOGY

OVARIAN GERM CELL TUMORS



Nests of clear cells, intervening fibrous strands



Large polygonal tumor cells; lymphocytes

DYSGERMINOMA

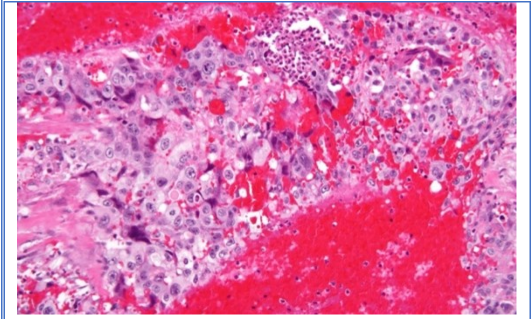
MORPHOLOGY

- Predominantly solid; may show cystic degeneration, hemorrhage, necrosis
- Cut surface is **lobulated, fleshy, yellow or cream colored**
- Calcified areas may indicate foci of gonadoblastoma
- **Sheets or nested arrangement**
- Tumor cells are **polygonal** with **well-defined cell membranes** and abundant clear or eosinophilic cytoplasm
- Nests of cells separated by **thin fibrous septae containing lymphocytes**
- May show granulomas or foci of spermatocytic tumor-like areas

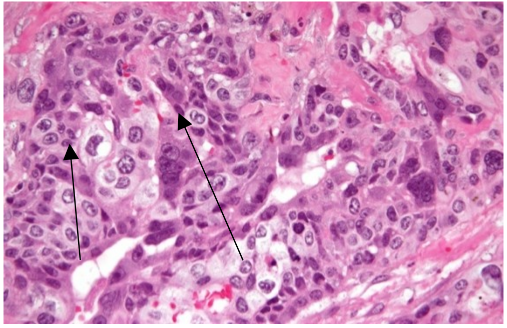
OTHER HIGH YIELD POINTS

- **Most common malignant germ cell tumor** (in testes = seminoma)
- Commonly seen in **children and young women**; usually **unilateral**
- **Elevated serum LDH**; rarely, serum βhCG may be elevated
- Can be associated with **paraneoplastic hypercalcemia**
- IHC: (+) SALL4, OCT4, LIN28, NANOG, KIT, D2-40
  (-) EMA, CD30, glypican-3
- **Very good survival**; recurrence seen in ~10% of cases
- Chromosome 12 abnormalities are most common and include **isochromosome 12p or 12p amplification**
- Less commonly, *KIT* mutations can be seen

Path Presenter



Solid with large areas of hemorrhage and necrosis



Cytotrophoblasts & syncytiotrophoblasts
Images contributed by Michael Bonert MD (Wikimedia)

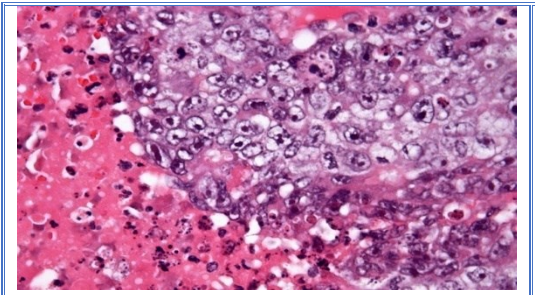
CHORIOCARCINOMA

MORPHOLOGY

- Solid with **large areas of hemorrhage and necrosis**
- **Admixture** of cytotrophoblasts (pale/clear cytoplasm), syncytiotrophoblasts (basophilic, multinucleated), and intermediate trophoblasts
- Extensive **hemorrhage and necrosis**

OTHER HIGH YIELD POINTS

- Rare primary ovarian tumor (<1%)
- **Non-gestational choriocarcinoma** commonly in **children, young women**
  - ➢ Rarely, somatically derived chorioca elements seen in older women
  - ➢ Difficult to treat
- **Gestational choriocarcinoma**, occur after puberty
  - ➢ Develops after ovarian pregnancy (i.e., ectopic pregnancy)
  - ➢ Easier to treat
- **Serum βhCG is often elevated,** AFP levels may be elevated
- ~50% present with **precocious puberty**
- Metastases common at initial presentation: lungs, liver, bone, viscera
- IHC: **(+) hCG**
- **STR DNA genotyping** can be used to distinguish non-gestational choriocarcinoma from an ovarian metastasis of uterine or tubal gestational choriocarcinoma:
  - ➢ **Non-gestational choriocarcinoma** shows allelic pattern identical to that of the patient’s normal tissue
  - ➢ **Gestational choriocarcinoma** shows non-maternal alleles of paternal origin



Pleomorphic cells arranged in solid, nested pattern
Image contributed by Michael Bonert MD (Wikimedia)

EMBRYONAL CARCINOMA

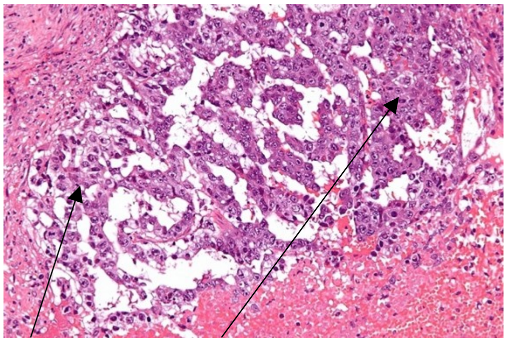
MORPHOLOGY

- Solid with areas of **hemorrhage and necrosis**
- Variable arhictectures: solid, nested, glandular and papillary patterns
- Polygonal cells with amphophilic or clear cytoplasm
- **Hyperchromatic, markedly atypical nuclei with prominent nucleoli**

OTHER HIGH YIELD POINTS

- Pure embryonal carcinoma occurs in **children and young women** with average age of 12-15 years; rare in older adults; unilateral
- Can present with **endocrine abnormalities** such as precocious puberty and menstrual irregularities
- **Serum βhCG** and/or **AFP** levels may be elevated
- **Pure embryonal carcinomas are very rare**; most commonly as a component of mixed germ cell tumor
- IHC: (+) **CD30**, OCT4, SALL4, SOX2, and LIN28

Mixed Germ cell tumor



Yolk sac tumor, embryonal carcinoma
Image contributed by Michael Bonert MD (Wikimedia)

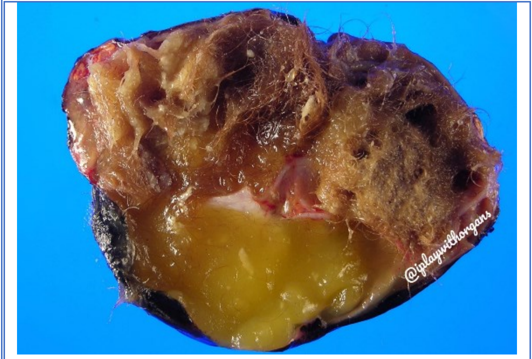
YOLK SAC TUMOR

MORPHOLOGY

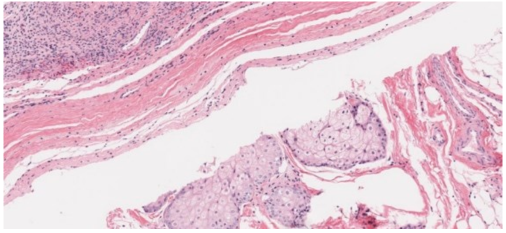
- Solid and cystic, friable with areas of **hemorrhage and necrosis**
- Most characteristic pattern is **endodermal sinus pattern** (Schiller-Duval bodies); other patterns include:
  - Reticular/microcystic, papillary, solid, festoon, and glandular
  - *Uncommon*: polyvesciular-vitelline, parietal, mesenchyme-like, hepatoid
- Cells show variable atypia, clear cytoplasm with hyaline globules

OTHER HIGH YIELD POINTS

- Reflects **endodermal extraembryonic differentiation**
- Occurs mostly in the **2nd and 3rd decades** of life; unilateral
- **Elevated serum AFP**
- May coexist with ovarian or endometrial cancer in older patients
- IHC: (+) **SALL4**, LIN28, **AFP**, glypican-3, ZBTB16, **CDX2** in **intestinal** pattern, **HepPar-1** in **hepatoid** pattern, **TTF-1** in **respiratory** pattern



Teratoma with sebaceous material and hair
Image courtesy of Cory Nash, MS, PA(ASCP)



Mesodermal and ectodermal elements within ovary

MATURE TERATOMA

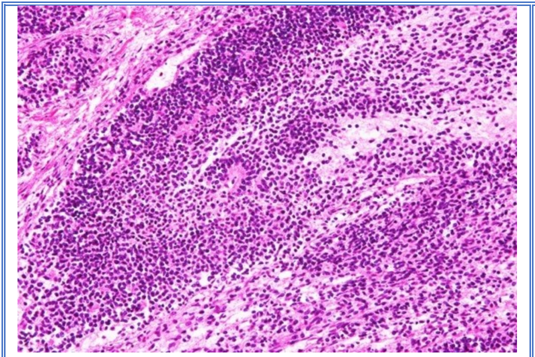
MORPHOLOGY

- Cystic and containing **sebaceous material, hair** and less commonly **teeth and cartilage** are seen grossly
  - **Rokitansky protuberance***:* solid nodule lined by hair-bearing skin
  - **Fetiform teratoma:** resembling a malformed human fetus
  - Grossing guidelines: sample solid areas at **one section per cm**
- Derivatives of **two or more germ cell layers** seen:
  - **Ectodermal** derivatives: squamous epithelium, cutaneous adnexal structures, neurectoderm (glia, ependymal, cerebellum)
  - **Mesodermal** derivatives: adipose tissue, bone, smooth muscle
  - **Endodermal** derivatives: gastrointestinal/respiratory epithelial lining, adrenal, parathyroid, thyroid, salivary glands, etc.
- Rare microscopic foci of immature neural tissue ≠ immature teratoma

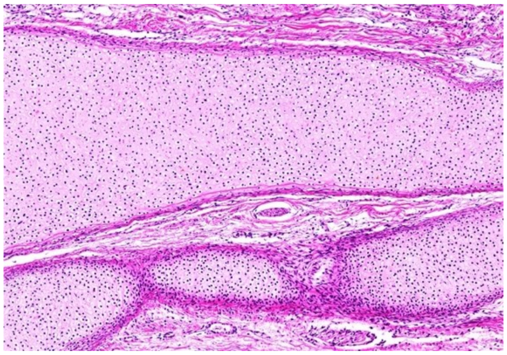
OTHER HIGH YIELD POINTS

- Almost always benign; mostly unilateral (10% bilateral)
- **Malignant transformation***:* rare; occurs as somatic neoplasm arising from a teratoma, **most commonly squamous cell carcinoma**
- **Gliomatosis peritonei***:* can occur in patients with mature teratoma; does not adversely affect the prognosis
- Presence of rare microscopic foci of neural tissue does not adversely affect prognosis

Path Presenter



Neuroectodermal tubules and rosettes



Immature bone (images courtesy @Patholwalker, Twitter)

IMMATURE TERATOMA

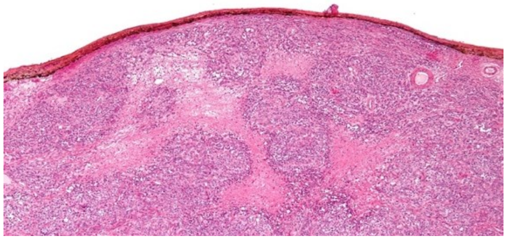
MORPHOLOGY

- **Large, fleshy, grey-tan, solid-cystic**, areas with **hemorrhage and necrosis**
- **MUST show immature tissues;** amount and type is variable
- Most commonly **neuroectodermal tubules and rosettes** can be seen, comprised of mitotically active, hyperchromatic, small cells
- Immature mesodermal or endodermal components can also be seen
- Trabecular pattern of blood vessels can be present, and may resemble a vascular tumor
- **Grading** - number of low-power fields with immature neuroepithelium:
  - Grade 1: ≤1 low power field of immature neuroepithelium
  - Grade 2: 2-3 low power fields of immature neuroepithelium
  - Grade 3: >3 low power fields of immature neuroepithelium
  - Metastatic sites are graded using the same criteria
  - **Pure gliomatosis peritonei is considered mature (Grade 0)**
- **Ectodermal** derivatives: squamous epithelium, cutaneous adnexal structures, neurectoderm (glia, ependymal cells, cerebellum)
- **Mesodermal** derivatives: adipose tissue, bone, smooth muscle
- **Endodermal** derivatives: gastrointestinal/respiratory epithelial lining, adrenal, parathyroid, thyroid, salivary glands, etc.

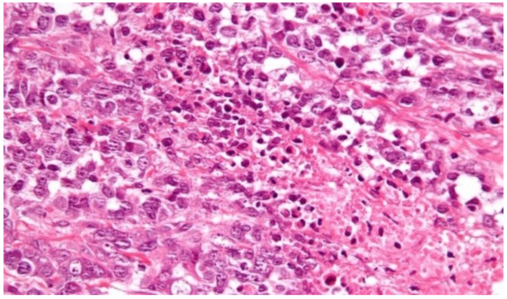
OTHER HIGH YIELD POINTS

- **Second most common malignant germ cell tumor in the US**
- Commonly presents in the **first 3 decades of life; unilateral**
- Malignant counterpart of mature teratoma
- **Growing teratoma syndrome:** extraovarian deposits of mature teratoma tissue seen in patients of immature teratoma after chemotherapy

Nests and sheets of small cells, areas of necrosis



Small cells with vesicular chromatin, necrosis



Images contributed by Michael Bonert MD (Wikimedia)

SMALL CELL CARCINOMA, HYPERCALCEMIC TYPE (SCCHT)

MORPHOLOGY

- **Large, fleshy, tan-white to grey** with areas of hemorrhage, necrosis, and cystic degeneration
- Cells are small with scant cytoplasm, and monomorphic round, ovoid or spindled nuclei with vesicular chromatin, small nucleoli
- **Mitoses are brisk**
- Large cells can be present in various numbers: have abundant cytoplasm with eccentric nuclei with prominent nucleoli
- 15% cases have a minor mucinous component consisting of benign glands, cysts, or rarely signet ring cells

OTHER HIGH YIELD POINTS

- Rare tumor occurring **exclusively in women of the reproductive age** group and children with a mean age of 25 years
- Familial cases occur at a younger age, bilateral
- Associated with **paraneoplastic hypercalcemia** in two-third cases
- IHC: (+) WT1, p53, and p16; (+/-) neuroendocrine markers, CD10, EMA, PTHrP; **loss of SMARCA4**
- Somatic or germline mutations in ***SMARCA4***
- **Favorable prognostic factors**: age >30 years, normal calcium levels, tumor size < 10 cm, absence of large cells

GONADOBLASTOMA

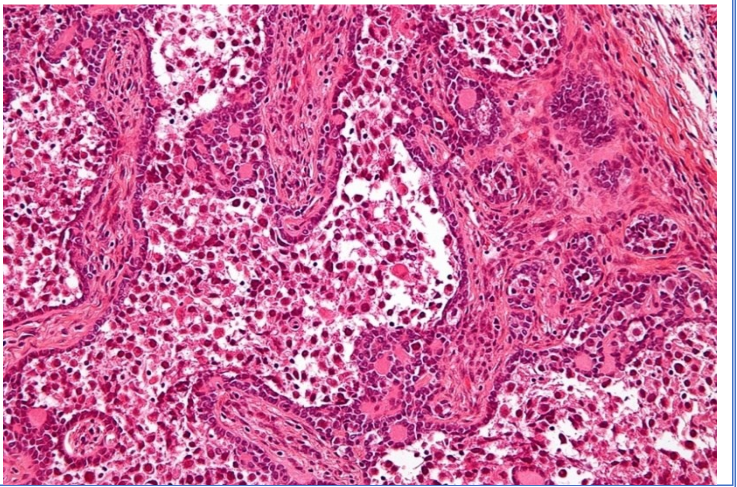
MORPHOLOGY

- Ill-defined with **tan to grey areas** with a **gritty texture**
- **Round nests** composed of **3 elements**: germ cells, small sex cord cells, and globular basement membrane deposits
- Occasional cases show large, anastomosing nests resembling germinoma

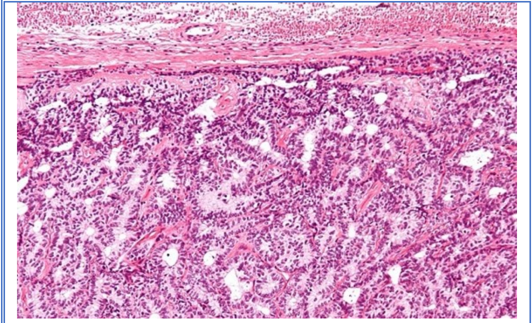
- **Testis or streak gonads can be seen at the periphery**
- Can show areas of invasive germinoma and other invasive germ cell tumors
- **Dissecting gonadoblastoma/undifferentiated gonadal tissue:** areas surrounding tumor with corded pattern of same components

OTHER HIGH YIELD POINTS

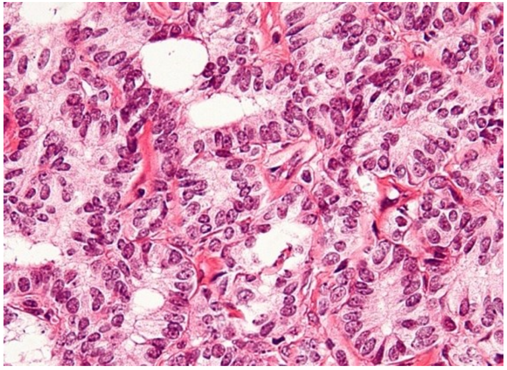
- Rare tumor restricted to **patients with gonadal maldevelopment**
    - **Dysgenetic gonads** lead to gonadoblastoma in 50-60% cases
- A form of in situ germ cell neoplasia, similar to germ cell neoplasia in situ (GCNIS) in the testis
- **Wide age range**: neonatal to 4th decade
- Most patients are **phenotypically female**; 50% patients appear as virilized females, 30% non-virilized females, and 20% as males with hypospadias and cryptorchidism
- Can be seen as part of **various tumor syndromes**: Denys Drash syndrome, Frasier syndrome, Swyer syndrome, Turner syndrome, androgen insensitivity syndrome
- IHC: Germ cells (+) **OCT3/4**, podoplanin, PLAP
  Sex cord cells (+) inhibin, calretinin, SF1, FOXL2, (weak) SOX9
- Pathogenesis: delayed maturation of germ cells with inadequate expression of SOX9 and enhanced KIT/KITLG signaling
- Activating *KIT* mutations are seen in >50% cases
- Bilateral gonadectomy is recommended because of high risk of contralateral gonadoblastoma



Composed of Sertoli cells, granulosa cells and primitive germ cells
Image contributed by Michael Bonert MD (Wikimedia)



Wolffian tumor; bland nuclei without nucleoli



Images contributed by Michael Bonert MD (Wikimedia)

WOLFFIAN TUMOR

MORPHOLOGY

- Can be **solid or cystic** with **lobulated, tan-white** cut surface
- Varying proportions of **4 distinct patterns**:
    - **Diffuse/solid** with a spindle cell population
    - **Tubular** pattern: lined by columnar cells with basal nuclei and compressed tubule with a slit-like lumen
    - **Retiform** (sieve-like): network of elongated and branching tubules
    - **Multicystic**: lined by single layer of flattened cells
- Nuclei are bland without nucleoli
- Low mitotic count

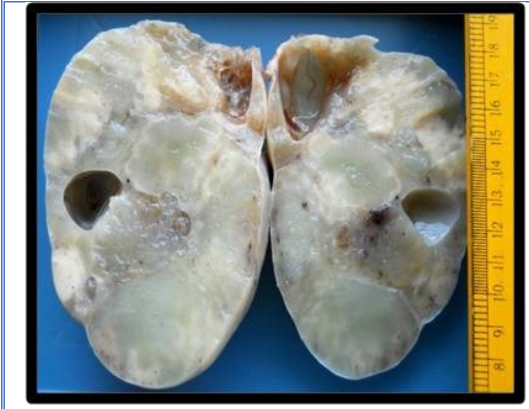
OTHER HIGH YIELD POINTS

- Also known as **female adnexal tumor of Wolffian origin (FATWO)**, Wolffian adenoma, and retiform Wolffian adenoma
- Derived from mesonephric remnants in the upper zone of the Wolffian system
- Patient age ranges from 18 to 83 years with a mean of 45 years
- **Very rare** ~100 cases described so far
- IHC: (+) AR, calretinin, inhibin, FOXL2, WT1, luminal CD10; (-) EMA
- Most have a **benign** behavior
    - One-fifth of tumors have a **more aggressive behavior with recurrences**, residual tumors, and liver & lung metastases → should be considered a tumor of low malignant potential

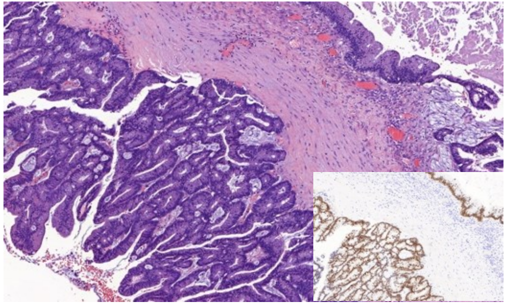
Seminoma **Embryonal Carcinoma** **Yolk Sac Tumor** **Choriocarcinoma**

SALL4	+	+	+	+
OCT3/4	+	+	-	-
D2-40	+	+/-	-	-
CD117	+	-	-	-
CD30	-	+	-/+	-
Glypican-3	-	-	+	+/-

METASTATIC LESIONS TO THE OVARY



Krukenberg tumor
Image courtesy Department of Pathology, Calicut Medical College (Wikimedia)



Metastatic colorectal carcinoma to the ovary
Inset: CDX-2 immunohistochemistry
Photocredit: Twitter @TristanRutland7

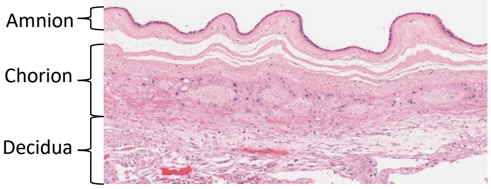
METASTASIS

- 3-30% of malignant ovarian tumors are metastatic
- **Ovary is the most common site of metastasis in the female genital trac**
- Can present synchronously or metachronously with the primary tumor
- **Most common** primary tumor to metastasize to the ovary is **colorectal adenocarcinoma**
  - Others include breast cancer, appendiceal carcinomas, endocervica endometrial, etc.
- **Mechanism:** direct extension, lymphovascular/hematogenous, transcoelomic/transperitoneal, or transtubal

MORPHOLOGY

- Features that **favor metastasis**:
  - Bilaterality
  - Small tumor size (< 10-13 cm)
  - Nodular growth pattern
  - Presence of tumor on the surface and/or superficial cortex of ovary
  - Presence of extraovarian metastatic disease
- **Infiltrative** growth pattern with **desmoplastic reaction**
- Nodular growth pattern
- Involvement of surface and superficial cortex
- Presence of **signet ring cells** strongly favors metastasis
- Other features specific to the primary tumor:
  - Garland pattern with dirty necrosis: **colorectal adenocarcinoma**
  - Tall mucin rich cells, dissecting mucin, pseudomyxoma peritonei: **appendiceal neoplasm**
  - Single file cords: **lobular carcinoma breast**

PLACENTA

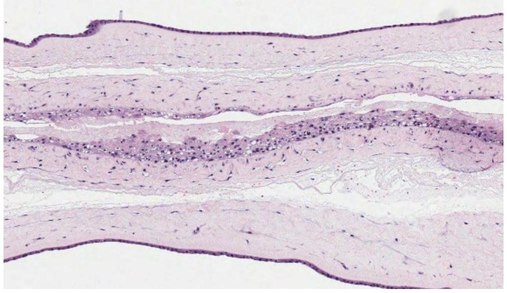


NORMAL HISTOLOGY

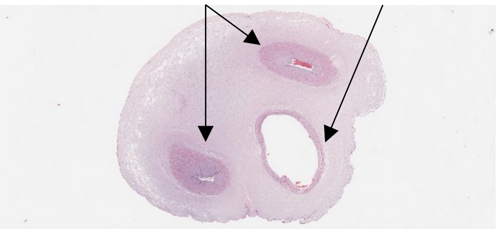
PLACENTAL MEMBRANES

- **Amnion** – innermost layer lined by single layer of epithelium with underlying connective tissue
  - Can see squamous hyperplasia with hyperkeratosis as an incidental finding associated with irritation
  - Sometimes separated from chorion by an artifactual gap
- **Chorion** – connective tissue with fetal vasculature
- **Decidua** – decidualized (due to progesterone) endometrial stroma with polygonal cells with abundant pink cytoplasm and large open nuclei
  - May have hypersecretory glandular epithelium (Arias-Stella reaction)
  - Rare white blood cells are considered normal
  - Maternal blood vessels
- **Twin intervening placental membranes**

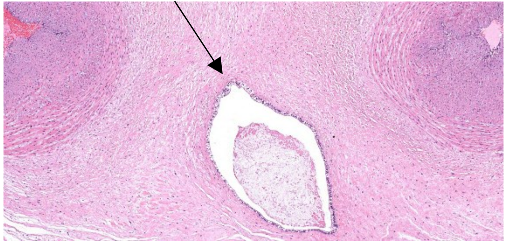
Twin (DiDi) placenta



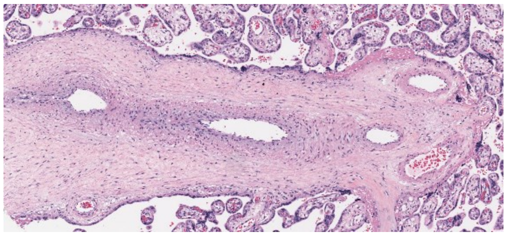
Umbilical cord with two arteries and one vein



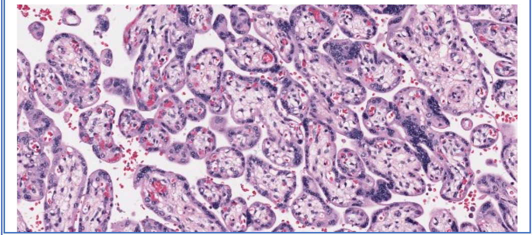
Persistent omphalomesenteric duct



Stem villi



Terminal villi



- Diamniotic, monochorionic (DiMo) placenta: no intervening chorionic layer; more common; shared vascularity in placental disc; possible twin-twin transfusion
- Diamniotic, dichorionic (DiDi) placenta: intervening chorionic layer; less common; vascular anastomoses uncommon

UMBILICAL CORD

- Covered by amniotic membrane with underlying Wharton's jelly
- **Two umbilical arteries**: carry deoxygenated blood from fetus to placenta
- **One umbilical vein**: carries oxygenated blood from placenta to fetus
- **Persistent omphalomesenteric (vitelline) duct**: derived from yolk sac; small tubular structure lined by mucin-secreting epithelium
- **Persistent allantoic duct**: derived from allantois; small tube with epithelium resembling urothelium located between arteries

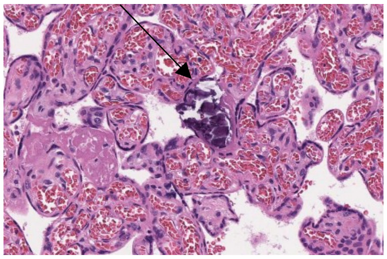
PLACENTAL DISC

- **Stem villi** – transport blood from chorionic vessels to smaller villi; trophoblastic covering collagenous stroma and large fetal vessels; hierarchical branching to smaller villi to allow nutrient/waste exchange
- **Terminal villi** – appearance ("maturity") changes with gestational age to facilitate oxygen exchange; covered by syncytiotrophoblasts and cytotrophoblasts; later gestational age placentas show more peripheral vasculature

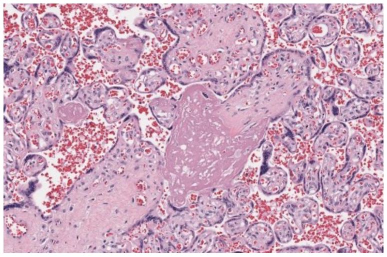
NORMAL DISC FINDINGS IN *TERM* PLACENTAS

- **Scattered coarse calcifications** within or adjacent to villi (abnormal if very dramatic or premature birth)
- **Small infarcts** (abnormal if premature birth or >3 cm)
- **Moderate amounts of perivillous fibrin** (<25%)
- **Fresh retroplacental blood clot** that is easily detached and not associated with infarct or placental compression

Coarse calcification

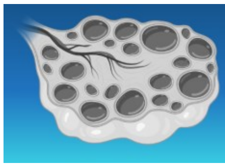


Moderate perivillous fibrin



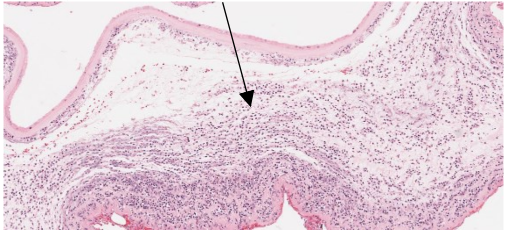
AMNIONIC FLUID INFECTION

- Usually results from ascending infection after premature rupture of membranes (before labor)
- Common pathogens: Ureaplasma, Fusobacterium, Bacterioides, mixed gram-positive anaerobes, E. coli, Group B Streptococcus, S. pneumoniae
- Amniotic fluid infection associated with extreme preterm delivery in mid-gestation raises concern for cervical incompetence

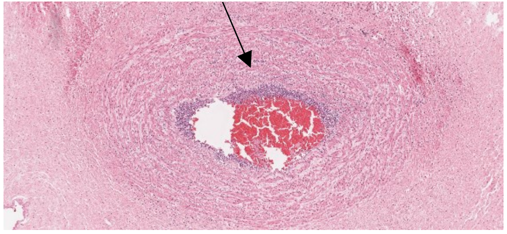


15. GYNECOLOGIC PATHOLOGY

Neutrophils in the chorioamnion



Neutrophils within the umbilical vein



CHORIOAMNIONITIS

MORPHOLOGY

- **Acute inflammation** in the **chorion or chorioamnion**
- Scattered neutrophils are a non-specific finding in the decidua
- **Subchorionitis**: dense neutrophil infiltrate in the decidua (earliest stage of maternal inflammatory response)

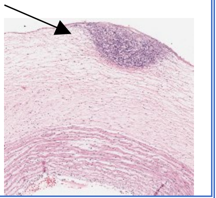
OTHER HIGH YIELD POINTS

- **Maternal response** to infection

FUNISITIS

MORPHOLOGY

- **Acute inflammation** of the **umbilical cord and umbilical vessels**
- Candida infection associated with surface inflammation
- Can see toxoplasmosis organisms in Wharton's jelly



OTHER HIGH YIELD POINTS

- **Fetal response** to infection

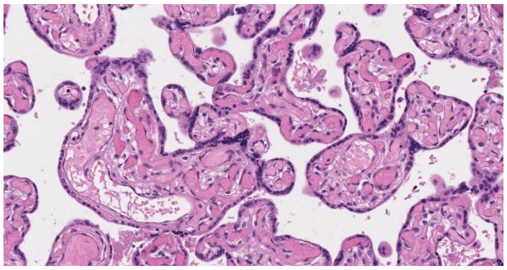
Link Link Link

STAGING AND GRADING OF MATERNAL AND FETAL INFLAMMATORY RESPONSES	
MATERNAL RESPONSE	
Stage 1 – acute subchorionitis/chorionitis **Stage 2 – acute chorioamnionitis** **Stage 3 – necrotizing chorioamnionitis**	Grade 1 – not severe Grade 2 – severe with confluent neutrophils or subchorionic microabscesses
FETAL RESPONSE	
Stage 1 – chorionic vasculitis or umbilical phlebitis **Stage 2 – involvement of umbilical vein and ≥1 umbilical artery** **Stage 3 – necrotizing funisitis**	Grade 1 – not severe Grade 2 – severe with near confluent intramural neutrophils and attenuation of vascular smooth muscle

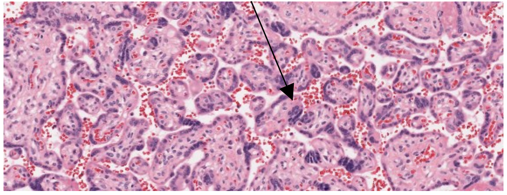
UTEROPLACENTAL UNDERPERFUSION

- Also known as "Maternal Vascular Malperfusion"
- Changes associated with chronic suboptimal uterine-to-placental blood flow
- Caused by maternal conditions: pre-eclampsia, hypertension, diabetes, autoimmune disease (e.g., SLE and anti-phospholipid antibody syndrome), abnormal uterine anatomy, etc.
- Gross findings: small placenta, infarction, retroplacental hemorrhage
- Often associated with fetal growth restriction and preterm labor; can recur in subsequent pregnancies

Immature terminal villi



Mature terminal villi, syncytial knots



VILLOUS MATURITY

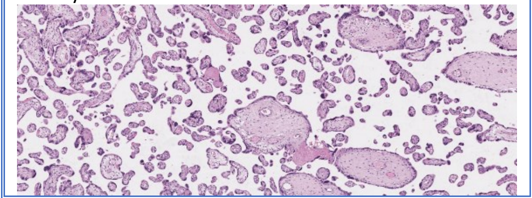
MORPHOLOGY

- **Immature terminal villi** (less efficient oxygen exchange):
  - Larger, more cellular, edematous with central capillaries
  - Evenly distributed trophoblastic covering
- **Mature terminal villi** (more efficient oxygen exchange):
  - Smaller, less cellular with peripheral capillaries
  - Condensed syncytiotrophoblasts with prominent **syncytial knots**

OTHER HIGH YIELD POINTS

- Increased villous maturation ("hypermaturation" or "accelerated villous maturation") is associated with chronic placental ischemia
- Should evaluate villous maturity closer to the maternal surface
- Maturity timeline:
  - 20-25 weeks – 25% immature
  - 26-32 weeks – 10% immature
  - 33-36 weeks – 5% immature
  - ≥37 weeks – 1% immature
- Syncytial knots on greater than 1/3 of villi in term placenta = **increased**

Paucity of terminal villi



DISTAL VILLOUS HYPOPLASIA

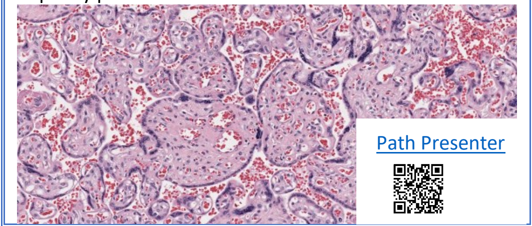
MORPHOLOGY

- Paucity of terminal villi in relation to the number of stem villi
- Villi are pencil-shaped (long and thin) with increased syncytial knots

OTHER HIGH YIELD POINTS

- More commonly seen with underperfusion early in pregnancy
- Evaluate villi towards maternal surface

Capillary proliferation within villi



Path Presenter

CHORANGIOSIS

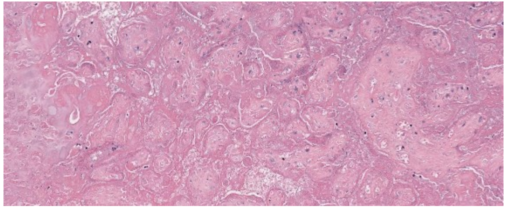
MORPHOLOGY

- Fetal capillary proliferation defined by "rule of 10's":
  - **More than 10 capillary cross sections** present in **more than 10 contiguous villi** in **at least 4 placental regions**

OTHER HIGH YIELD POINTS

- Localized response to hypoxia due to low oxygen tension in maternal blood
- Seen with high altitude, diabetes, and pre-eclampsia

Ischemic necrosis with ghost villi (remote infarct)

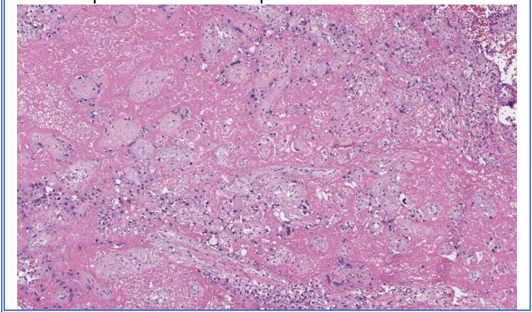


INFARCTS

MORPHOLOGY

- **Early infarcts**: crowded and congested villi (collapse of intervillous space from localized cessation of maternal blood flow), which may be hemorrhagic, and with early loss of nuclear staining
- **Remote infarcts**: ischemic necrosis with pyknosis and karyorrhexis, loss of nuclear staining, and eventual ghost villi
- Estimate percent size based on gross examination

Massive perivillous fibrin deposition



PERIVILLOUS FIBRIN

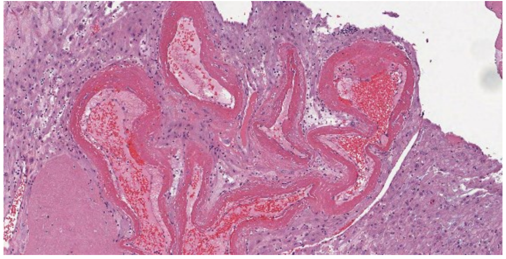
MORPHOLOGY

- Deposition of fibrin between villi
- Homogenous pink material with intact villous nuclear basophilia (as opposed to an infarct, in which everything is homogenously pink with coagulative necrosis)
- Can be intervillous or nodular

OTHER HIGH YIELD POINTS

- Normal finding in term placenta if <25% of volume
- If >25% → Massive perivillous fibrin deposition
  - Potentially compromises fetal perfusion → worse outcome

Fibrinoid necrosis (severe decidual arteriopathy)



DECIDUAL ARTERIOPATHY

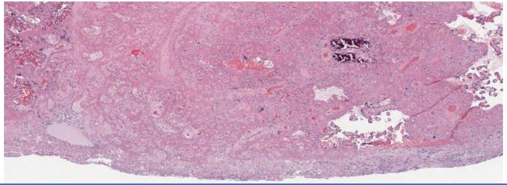
MORPHOLOGY

- **Mild decidual arteriopathy** – retention of smooth muscle in arterial walls
- **Severe decidual arteriopathy** – fibrinoid necrosis of spiral arterioles (eosinophilic material in vessel wall); can be associated with foamy macrophages (atherosis) and lymphocytes

OTHER HIGH YIELD POINTS

- Occurs with failed normal conversion of maternal spiral arterioles into amuscular, low-resistance vessels
- Associated with maternal hypertension, autoimmune diseases, and pre-eclampsia

Maternal floor infarct with increased fibrin deposition



MATERNAL FLOOR INFARCT

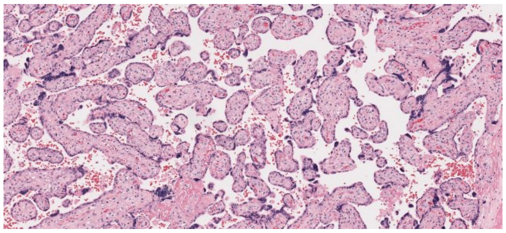
MORPHOLOGY

- **Grossly visible white rind** on maternal surface
- **Extensive fibrin deposition** in the decidua/intervillous space

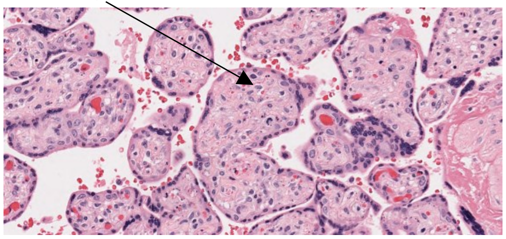
OTHER HIGH YIELD POINTS

- Similar to massive villous fibrin deposition and associated with poor outcomes

Multifocal avascular villi



Villous karyorrhexis



FETAL VASCULAR MALPERFUSION

MORPHOLOGY

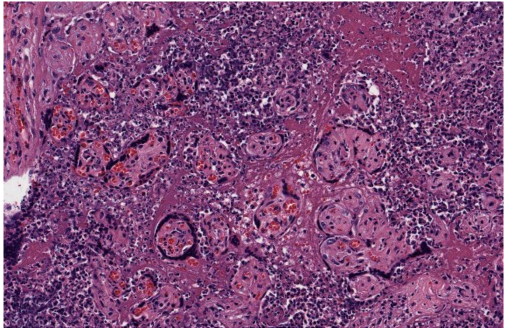
- Thrombosis, avascular villi, vascular obliteration, and villous karyorrhexis

OTHER HIGH YIELD POINTS

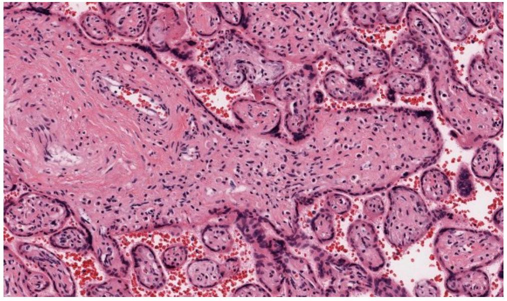
- Formerly “fetal thrombotic vasculopathy”
- Occurs **secondary to obstruction of fetal blood flow** (antemortem or postmortem)
- **Antemortem changes are focal or multifocal:**
  - Can result from umbilical cord lesions, hypercoagulability, maternal diabetes, and fetal cardiac dysfunction
  - Can result in intrauterine growth restriction (IUGR)
- **Postmortem changes are global:**
  - Diffuse loss of vascularity is seen with passive involutional changes seen after fetal death

Path Presenter

Acute necrotizing villitis and intervillitis



Lymphohistiocytic infiltrates in chronic villitis



ACUTE VILLITIS

MORPHOLOGY

- **Neutrophils in villi and intervillous space**
- Can form **microabscesses**

OTHER HIGH YIELD POINTS

- Strongly associated with **maternal bacteremia**
- Common pathogens: **Listeria, Group B Strep, Syphilis**

CHRONIC VILLITIS

MORPHOLOGY

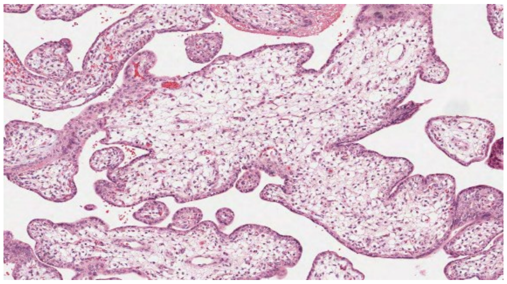
- Mostly **histiocytes** with **scattered lymphocytes** in villi
- If many giant cells are present → “granulomatous villitis”
  - Despite the name, true granulomas are often not present

OTHER HIGH YIELD POINTS

- **Majority (90%) due to abnormal immune reaction**:
  - maternal T-cells to fetal antigens, termed “villitis of unknown etiology” (VUE)
  - Can recur with subsequent pregnancies
  - If severe, can cause IUGR or even fetal demise
- **Minority (10%) due to TORCH infection**, usually **CMV**
  - Get Gram, GMS, AFB, CMV, and syphilis stains

Path Presenter

Chronic villous edema



VILLOUS EDEMA

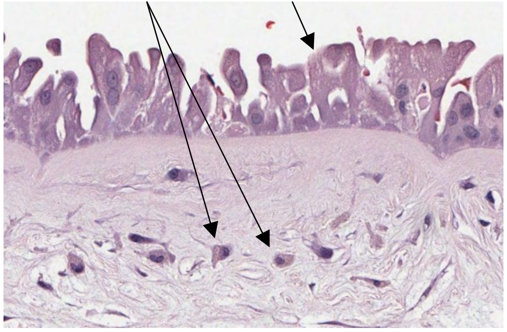
ACUTE VILLOUS EDEMA

- Patchy villi with round loculations of watery fluid
- Commonly accompanies chorioamnionitis but can be seen in many settings

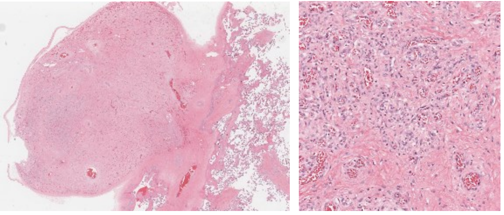
CHRONIC VILLOUS EDEMA

- **Diffusely enlarged villi** with clear, watery, hypocellular stroma
- Associated with **fetal hydrops**
- **Common causes**: fetal cardiovascular disease, fetal aneuploidy, fetal thoracic anomalies, severe fetal anemia, and complications from twinning
- Less common (now): immune-mediated hydrops from maternal antibodies against fetal red blood cells (Rh-mediated)

Meconium histiocytes and reactive amnion



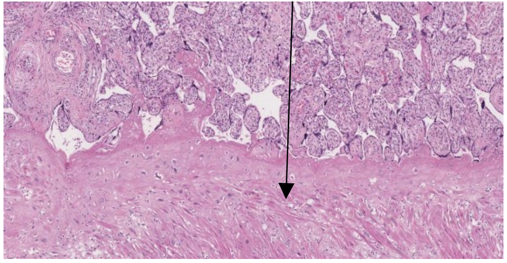
Chorangioma



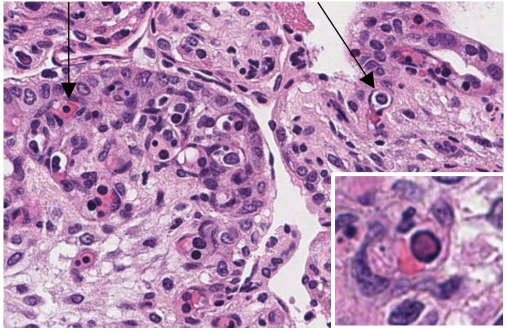
Well-circumscribed nodule

Capillary proliferation

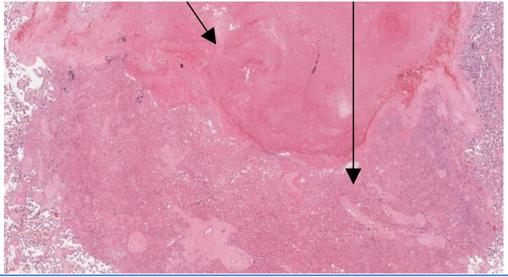
Villi in direct contact with myometrium (placenta accreta)



Nucleated RBCs, some with parvovirus inclusions



Retroplacental hemorrhage with compression of villi



OTHER PLACENTAL FINDINGS

MECONIUM

- Orange-brown non-refractile pigment in macrophages
- Derived from first infant stool, if voided in utero
- Potential sign of fetal distress
- Can cause meconium aspiration syndrome or chorionic vascular necrosis
- Often associated with reactive and/or necrotic amnion (look for blue-gray myxoid amnionic-chorionic cleft)
- Often best to correlate with clinical and gross findings because other pigments (i.e., hemosiderin) can be present

CHORANGIOMA

- Relatively common; benign placental "tumor"
- Well-circumscribed, expansile nodule of capillary proliferation with a continuous layer of pericytes within a stem villous
- Can be grossly visible
- Similar staining profile as infantile hemangioma: IHC (+) GLUT-1
- Large lesions (>4 cm) can cause fetal morbidity such as thrombocytopenia and shunting
- Associated with fetal hemangiomas and twins

PLACENTA CRETA

- Decidua is deficient or absent, at least focally
- Villi come into **direct contact with myometrium**
- **Placenta accreta** – villi touch myometrial surface directly
- **Placenta increta** – villi invade into myometrium
- **Placenta percreta** – villi invade completely through uterine wall to peritoneum or other structures
- Increta and percreta may in part be due to uterine anomalies like scarring or thin myometrium
- Trophoblasts stain with cytokeratin IHC, which can be helpful to determine if villi are touching muscle (versus decidualized stromal cells)

SINGLE UMBILICAL ARTERY

- Frequently seen in the context of other anomalies, often urinary tract/kidney and heart anomalies
- Increased risk of stillbirth and death

FETAL CAPILLARY RUPTURE

- Also known as "intravillous hemorrhage"
- **Hemorrhage into interstitium of villi** ("bags of blood")
- Due to **placental trauma** (e.g., manual extraction, cesarean section, acute abruption, etc.)

PARVOVIRUS INFECTION

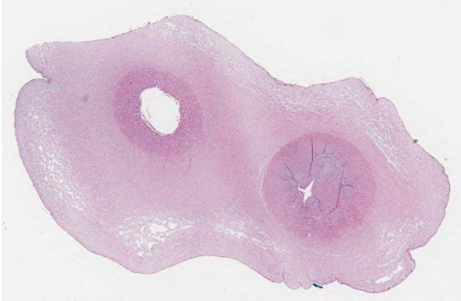
- Characteristic **violet, glassy, intranuclear inclusions in erythroblasts**
- **Parvovirus infect RBCs** → hemolysis and transient erythroid aplasia
- Fetus often dies from anemia or hydrops
- Often see placenta hydrops; no inflammatory response

RETROPLACENTAL HEMORRHAGE

- Pathologic term for the clinical entity of **placental abruption**
- Blood accumulation beneath/dissecting the decidua with compression of the overlying villi → villous crowding, congestion, intravillous hemorrhage
- Associated with infarction; hemosiderin present after a few days

Link Link Link

MICROSCOPIC APPROACH TO THE PLACENTA


Umbilical cord with single umbilical artery

1. EVALUATE MEMBRANES ROLLS

- **Inflammation** – look for neutrophils in chorioamnion → chorioamnionitis
- **Vascular changes** – spiral arteries should have NO muscle and thin walls
  - If retained muscle layer → mild decidual arteriopathy
  - If fibrinoid necrosis → severe decidual arteriopathy
- **Abruption** – retromembranous hemorrhage in varying states of organization
- **Pigment** – look for meconium (faint yellow-orange-brown) in macrophages
  - Look for reactive reactive-appearing amniotic cells as a clue

2. EVALUATE UMBILICAL CORD

- Count the **number of vessels** – should be two arteries and one vein
- **Inflammation** – look for neutrophils in/around vessels → funisitis
- **Thrombosis** – look for vascular thromboses (rare)

3. EVALUATE DISC SURFACE

- Look for the same **surface inflammation and pigments** that you looked for in the membrane rolls
- **Vascular changes** – look at large surface fetal vessels for thrombosis; myocyte necrosis can be seen with meconium

4. EVALUATE STEM VILLI

- **Thrombosis** – look for vascular changes like thrombi or vascularization
- **Microorganisms** – look for viral inclusions
- **Fetal blood** – increased neutrophils or nucleated RBCs could indicate fetal infection/stress

5. EVALUATE TERMINAL VILLI

- **Look at maturity** – after 37 weeks, almost all villi should be mature terminal villi (small, peripheral capillaries, prominent syncytial knots); if mature but preterm, could be "hypermaturation" as seen with placental ischemia
- **Chorangiosis** – >10 capillaries in >10 contiguous villi → due to hypoxia
- **Infarcts** – coagulative necrosis with loss of basophilia
- **Acute villitis** – neutrophils in villi and intervillous space → suggests maternal bacteremia → get bug stains
- **Chronic villitis** – histiocytes with some lymphocytes and plasma cells → associated with either TORCH infection (get CMV/syphilis stains) or autoimmune villitis of unknown etiology (VUE)
- **Diffuse stromal edema** – look for clear, watery, hypocellular stroma → often caused by fetal hydrops
- **Avascular villi** – loss of capillary vessels with collagenization → due to interruption of fetal blood flow upstream
  - If multifocal, indicative of fetal thrombotic vasculopathy
- **Fetal capillary rupture** – intravillous hemorrhage due to trauma (e.g., manual extraction)

6. EVALUATE *BETWEEN* VILLI

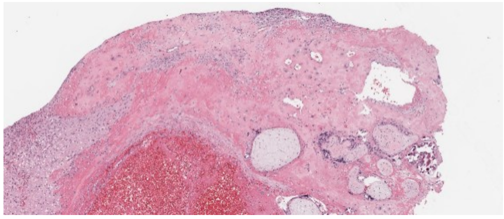
- **Collapse of intervillous space** – see with infarction of stem villi
- **Perivillous fibrin** – normal if <25%; otherwise, massive perivillous fibrin can compromise perfusion
- **Chronic histiocytic intervillousitis** – large numbers of mononuclear cells within the maternal intervillous space; associated with miscarriage, IURG, and fetal death

7. EVALUATE MATERNAL SURFACE

- **Maternal floor infarct** – appears as a white rind grossly; extensive fibrin deposition in the decidua
- **Decidual arteriopathy** – look for fibrinoid necrosis (same as step 1)
- **Hemorrhage** – large adherent clots with associated placental depression and ischemia (suggestive of abruption)
- **Villi on myometrium** – decidual deficiency, such as placenta creta

GESTATIONAL TROPHOBLASTIC DISEASE

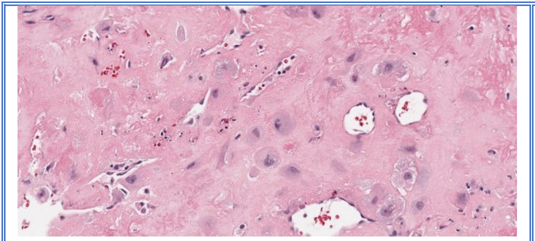
Small, circumscribed nodule


Intermediate trophoblasts in hyalinzed matrix

PLACENTAL SITE NODULE

MORPHOLOGY

- Well-circumscribed, usually <5 mm, lobulated
- Intermediate trophoblasts embedded in **abundant eosinophilic extensively hyalinized matrix**
- **Degenerated appearing** with lobulated hyperchromatic nuclei
- **Absent mitoses**
- If larger size, more cellular, and/or increased mitoses → consider "*Atypical Placental Site Nodule*" (precursor to epithelioid trophoblastic tumor)



OTHER HIGH YIELD POINTS

- **Benign**
- Often incidental finding in reproductive years after pregnancy (interval can be months to years)
- IHC (+) cytokeratin, p63, GATA-3, inhibin; low Ki67 (<5%)

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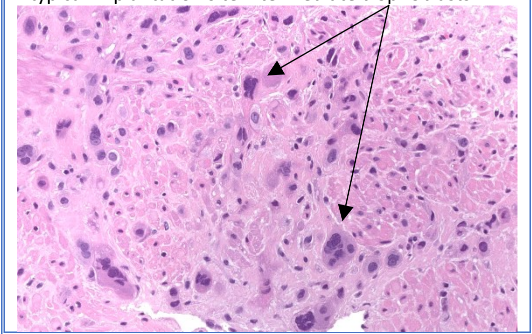


Atypical implantation site intermediate trophoblasts

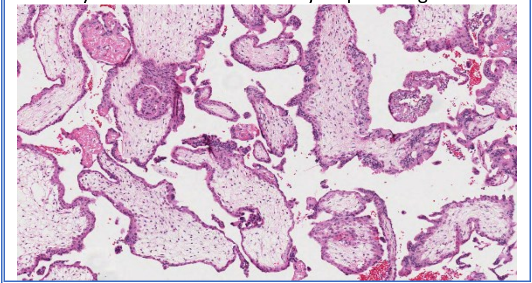
EXAGERRATED PLACENTAL SITE

MORPHOLOGY

- Unusually striking proliferation of implantation site intermediate trophoblasts
- Non mass forming but **infiltrative**
- Absent mitoses; low Ki67
- Can be cytologically **very atypical**

OTHER HIGH YIELD POINTS

- **Recent pregnancy**
- Physiologic and **regresses spontaneously**
- If no recent pregnancy, mass forming, destructive invasion, Ki67 >10%, consider *Placental Site Trophoblastic Tumor*



Similarly sized villi with variable hydropic change

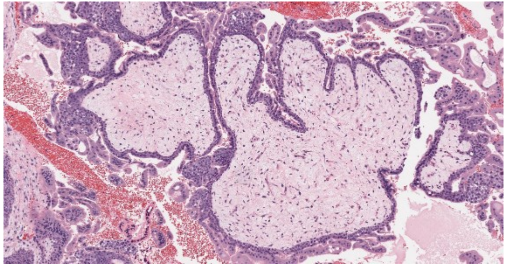
HYDROPIC ABORTUS

MORPHOLOGY

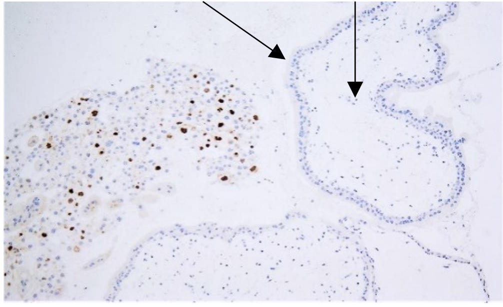
- **Early spontaneous abortion** with edematous placental tissue
- **Villi roughly the same size** with variable hydropic change
- **Cisterns rare/absent**
- **Trophoblasts often attenuated**
- Often hypovascular

OTHER HIGH YIELD POINTS

- Histologically resembles molar pregnancy
- Usually **scant tissue** (only 1-2 tissue blocks)



Cistern formation and trophoblastic proliferation



Loss of p57 in cytotrophoblasts and villous stroma

Photocredit: Twitter @Patholwalker (with permission)

COMPLETE HYDATIDIFORM MOLE

MORPHOLOGY

- Gross: **hydropic grape-like villi**
- **Diffusely hydropic villi**
- **Cistern formation** (fluid-filled cavities)
- **Irregular in size and shape** with club-like extensions
- Avascular – **no fetal RBCs**
- **Circumferential trophoblastic proliferation**
  - Cytotrophoblasts may have marked nuclear pleomorphism
  - Syncytiotrophoblasts can form lacy “medusa-head” festoons on the villous surface

OTHER HIGH YIELD POINTS

- Formed by anuclear ovum + sperm (either two sperm or one sperm that replicates) → **diploid and diandric** with two sets of paternal chromosomes (androgenetic diploidy)
- Clinical findings: **very high serum hCG** (>100k), large uterus, bleeding, “snowstorming” on ultrasound
- IHC: **absent/sparse (<10%) p57 nuclear staining** of cytotrophoblasts and villous stromal cells
- **Risk of choriocarcinoma** (<5%)
- Follow serum hCG for disease monitoring

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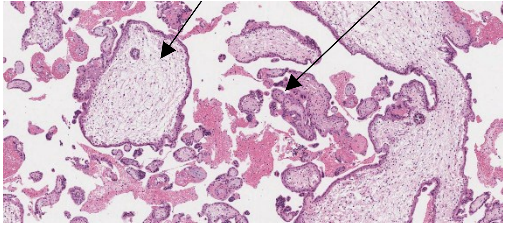
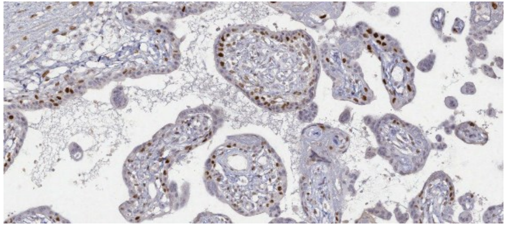
Two populations: hydropic villi and small fibrous villi



Retained nuclear p57



INCOMPLETE ("PARTIAL") HYDATIDIFORM MOLE

MORPHOLOGY

- Gross: unremarkable; gestational sac and/or fetal parts may be present
- **Two populations of villi:**
  - Enlarged, hydropic villi
  - Small/normal-sized fibrous villi
- **Irregular villi with scalloped borders** (think coast of Norway)
- Occasional cistern formation and trophoblastic proliferation (but less than complete mole)
- Stromal blood vessels with nucleated fetal RBCs

OTHER HIGH YIELD POINTS

- Usually **diandric triploidy** (one maternal and two paternal sets of chromosomes)
- Clinical findings: usually small uterus and normal/mildly elevated hCG
- IHC: **retained nuclear p57**
- Molecular: genotyping can confirm triploidy
- Usually **good outcome**; <1% risk of persistent disease or subsequent tumor

PERSISTENT MOLES

- Remaining molar tissue after original treatment (usually medication and curettage) → persistently elevated hCG
- Common causes:
  - **Invasive hydatidiform mole** – invades myometrium and/or uterine vessels (usually complete moles)
  - **Metastatic hydatidiform mole** – spread of abnormal chorionic villi to sites beyond the uterine cavity, most commonly vaginal wall/pelvis
- Usually effectively treated with chemotherapy

ABNORMAL (NON-MOLAR) LESIONS

- Descriptive diagnosis: **various non-molar villous lesions with features simulating partial mole**
  - Villous size irregularity, enlargement, mild trophoblastic proliferation
- Diverse origins: various chromosomal/genetic alterations; likely includes some hydropic abortions

	COMPLETE MOLE	PARTIAL MOLE	HYDROPIC ABORTUS
Amount of placental tissue (compared to normal)	Voluminous 5-10x increase	Moderately increased to normal	Scant
Villous size	Spectrum: large to small	Two populations	Mostly similar
Villous shape	Round to bulbous	Irregular (coast of Norway)	Round/smooth
Trophoblastic hyperplasia	Moderate to marked Often circumferential	Mild Rarely circumferential	Absent Polar
Cisterns	Common	Focal	Absent/inconspicuous
Villous stroma	Mucoid, hydropic, no fibrosis	Some fibrotic, some hydropic	Mostly hydropic, some fibrotic
Fetal tissue	Usually none	Usually present	Usually none
Fetal membranes	Rare	Common	Maybe
p57 nuclear staining*	Absent or sparse (<10%)	Retained	Retained
Ki67 of cytotrophoblasts	High (>70%)	High (>70%)	Low (<25%)
DNA content	Diploid (diandric)	Triploid (diandric, monogynic)	Diploid (bipaternal)
Chromosome number	46	60	46±

*Cytotrophoblasts and villous stromal cells

DIFFERENTIAL DIAGNOSES

VILLOUS ENLARGEMENT

- **Mesenchymal dysplasia** – stem villous size irregularity and enlargement (dysmorphic), vascular proliferation
- **Aneuploid gestation** – moderate villous enlargement, absence of cisterns, nucleated RBCs present
- **Incomplete (partial) mole** – two villous populations, absence of cisterns, nucleated RBCs present
- **Complete mole** – myxoid stroma, trophoblastic hyperplasia, absent/rare nucleated RBCs, villous stromal karyorrhexis

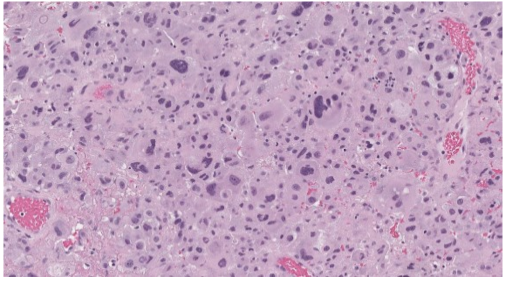
TROPHOBLAST HYPERPLASIA

- **Early gestation** – polarized (eccentric)
- **Incomplete (partial) mole** – minimal, syncytial, triploid
- **Complete mole** – variable hyperplasia, concentric, festooning, p57(-)

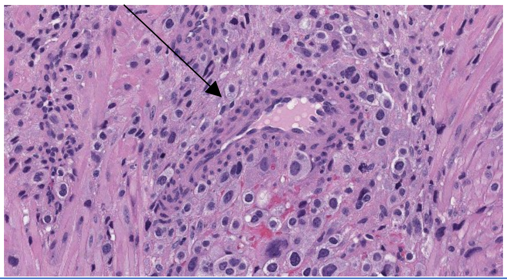
IMPLANTATION SITE ATYPIA

- **Early gestation** – mild nuclear hyperchromasia
- **Implantation site nodule** – lobulated, uniform nuclear spacing, low Ki67 (<5%)
- **Complete mole** – conspicuous atypia, minimal necrosis
- **Choriocarcinoma** – marked atypia, necrosis and hemorrhage, biphasic
- **Placental site/epithelioid trophoblastic tumor** – irregular/diffuse, scattered polyhedral cells, atypia, high Ki67 (>10%)

Large polyhedral cells. abundant amphophilic cytoplasm



Vascular infiltration

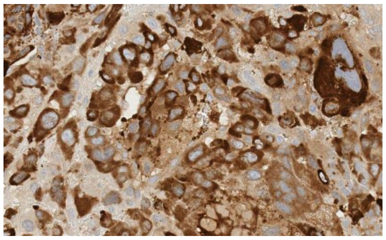


PLACENTAL SITE TROPHOBLASTIC TUMOR

MORPHOLOGY

- **Infiltrative** aggregates of **large, polyhedral** to round, predominantly mononuclear cells
- Scattered multinucleated cells
- **Abundant amphophilic to eosinophilic cytoplasm**
- Pronounced **nuclear atypia**
- **Infiltrates myometrium and vessels**

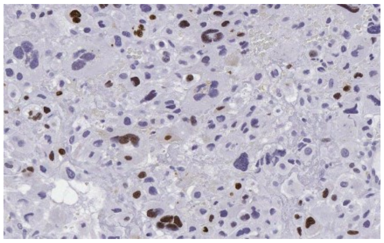
hPL



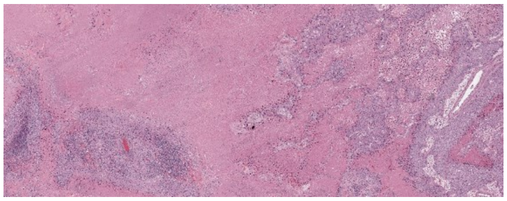
OTHER HIGH YIELD POINTS

- **Malignant**
- Derived from implantation site intermediate trophoblasts
- Mass-forming
- IHC (+) hPL, MUC4; Ki67 >10%

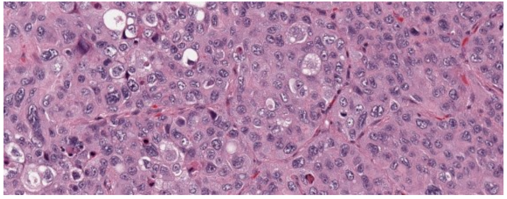
Ki67



Extensive necrosis



Uniform cells with granular eosinophilic cytoplasm



EPITHELIOID TROPHOBLASTIC TUMOR

MORPHOLOGY

- Well-circumscribed and destructive nodular proliferation of medium-sized trophoblastic cells
- **Uniform cells** with moderate amounts of **granular to clear eosinophilic cytoplasm** and round nuclei
- Distinct cell membranes; hyalin-like material
- Frequently extensive **necrosis**

OTHER HIGH YIELD POINTS

- **Malignant**; derived from chorionic-type intermediate trophoblasts
- Mass-forming
- IHC (+) p63, inhibin, GATA-3; Ki67 >10%

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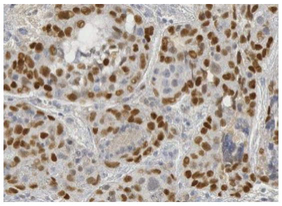
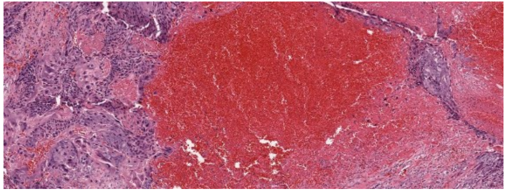
p63



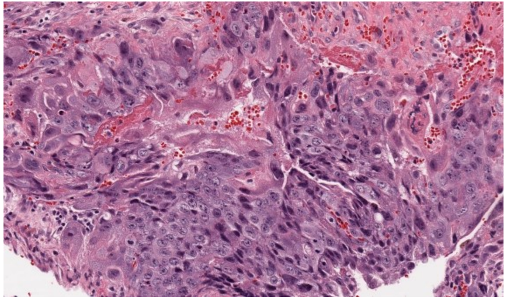
Extensive hemorrhage

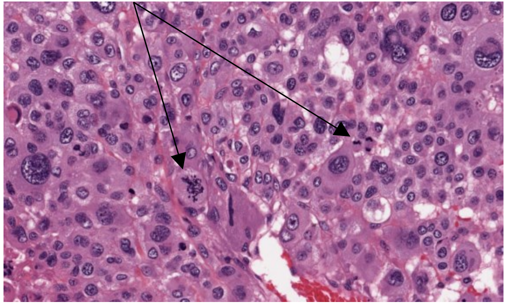


GESTATIONAL CHORIOCARCINOMA

MORPHOLOGY

- **Malignant cytotrophoblasts & trophoblasts (mononuclear) and syncytiotrophoblasts (multinuclear)**
- Abundant **hemorrhage**, necrosis, and lymphovascular invasion
- Marked **pleomorphism/atypia**
- Numerous **mitotic figures**
- Infiltrative, **destructive**, solid growth


Marked nuclear pleomorpishm


Significant mitotic activity

OTHER HIGH YIELD POINTS

- **Most common** gestational trophoblastic neoplasm
- **Elevated serum hCG**
- Can occur **after molar pregnancy (most common)**, normal pregnancy (intraplacental), or abortion
- Can be mixed with other tumors
- IHC (+) hCG, hPL, inhibin, SALL4, MUC4, p63; Ki67 >90%
- **Excellent response to chemotherapy**

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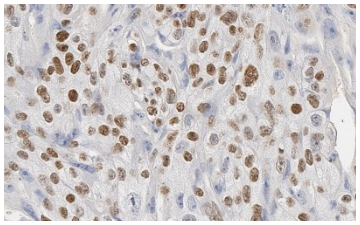
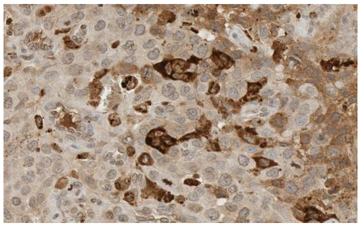
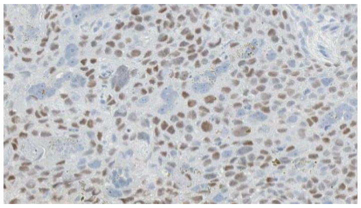
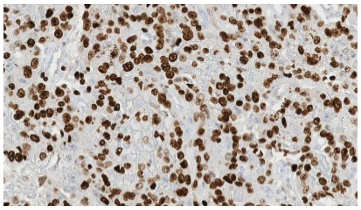
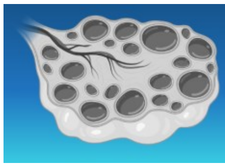

SALL4

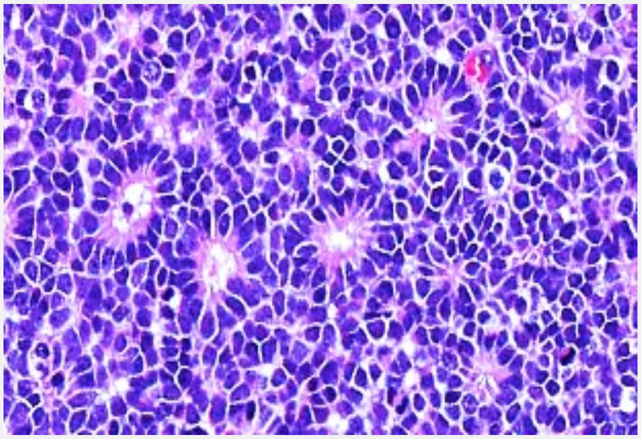

hCG


p63


Ki67



	Gestational choriocarcinoma	Non-gestational choriocarcinoma	Carcinoma with trophoblastic differentiation	Placental site trophoblastic tumor (PSTT)	Epithelioid trophoblastic tumor (ET)	Complete mole	Placental site nodule
Age	Reproductive age (~30 yo)	Children and young adults	Often post-menopausal	Usually reproductive age (~30 yo)			
Antecedent pregnancy	Mole or term (months to years later)	Unrelated	Unrelated	Term pregnancy (months to years later)		N/A	Yes (months to years later)
hCG (mIU/mL)	Elevated $>10 \times 10^3$	Elevated	Elevated	Elevated $>10 \times 10^3$	Elevated $>10 \times 10^3$	Markedly elevated	Not elevated
Gross appearance	Hemorrhagic mass			Solid mass		Absence of a mass lesion	
Location	Corpus	Usually ovary	Corpus			Usually endometrium	
Histology	Infiltrative tumor Bilaminar proliferation of mononuclear trophoblasts rimmed by multinucleated syncytiotrophoblasts Extensive hemorrhage, necrosis, atypia		Carcinoma of discernable differentiation Marked atypia often present	Infiltrating sheets invading myometrium Atypia	Pushing tumor Necrosis, hyalin-like material	Absence of atypia	Well-circumscribed No overt malignance
Tumor cells	Villous intermediate trophoblasts, syncytiotrophoblasts, and cytotrophoblasts		Poorly differentiated carcinoma with scattered hCG producing MNGCs	Implantation-type intermediate trophoblast	Chorionic-type intermediate trophoblast	Implantation-type intermediate trophoblast	Chorionic-type trophoblast
IHC	(+) hCG, SALL4, p63 Ki67 >90%		(+) hCG in MNGCs	(+) hPL Ki67 5-10% (-) SALL4	(+) p63 Ki67 >10% (-) SALL4	(+) hPL Ki67 <5% (-) SALL4	(+) hPL Ki67 <5%



Retinoblastoma (H&E stain), Flexner-Wintersteiner rosettes. Image courtesy: Akanksha Gupta, MD

CHAPTER 16: PEDIATRIC PATHOLOGY

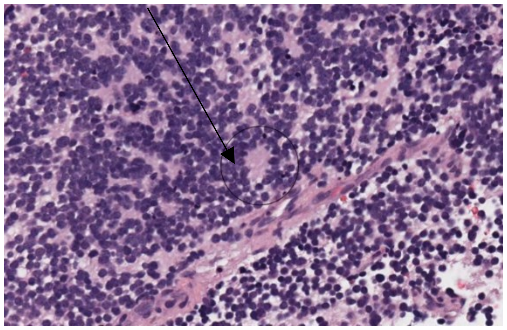
Jian Li, MD
Kannan Sivaraj, MD
Akanksha Gupta, MD

16. PEDIATRIC PATHOLOGY

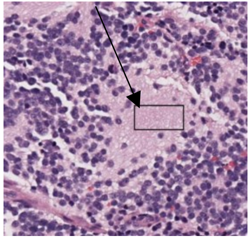
PEDIATRIC TUMORS

NEUROBLASTIC TUMORS

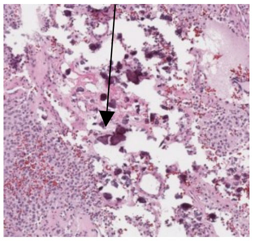
Rosettes



Neurofibrillary matrix



Calcification



NEUROBLASTOMA

MORPHOLOGY

- Peripheral neuroblastic tumors derive from the **sympathetic nervous system**, often in posterior mediastinum
- **Three subtypes** on grade of neuroblastic differentiation:
  - ➢ **Neuroblastoma, undifferentiated subtype:** SRBCT, needs IHC
  - ➢ **Neuroblastoma, poorly differentiated subtype:** <5% differentiation toward mature neurons, +/- Homer Wright rosettes, readily detectable neurofibrillary matrix, small to medium sized neuroblasts, salt and pepper chromatin, indiscernible / small amount of cytoplasm, vague cytoplasmic borders
  - ➢ **Neuroblastoma, differentiating subtype:** >5% differentiation toward mature neurons
  - ➢ **Large cell neuroblastoma:** Large open nuclei. Very prominent nucleoli indicating MYCN or MYC protein expression

OTHER HIGH YIELD POINTS

- **Most primitive/aggressive**, **malignant**, vast majority <5 years
- IHC: Schwann cells (+) S100, Ganglion cells (+) synaptophysin, NF

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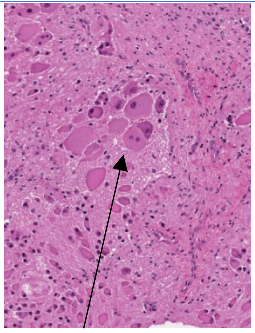
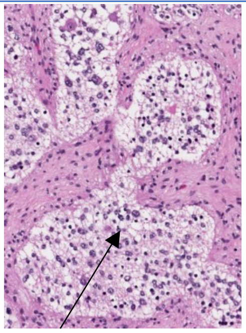


Ganglion cell



Neuroblastoma cell

GANGLIONEUROBLASTOMA

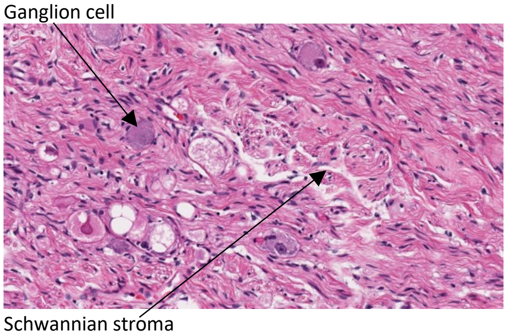
MORPHOLOGY

- Ganglioneuroblastoma, intermixed: Neuroblastic foci are randomly distributed
- Nodular Ganglioneuroblastoma: Grossly visible **nodular neuroblastic area with sharp demarcation**

OTHER HIGH YIELD POINTS

- Intermediate differentiation, malignant. IHC: Schwann cells (+) S100, Ganglion cells (+) Synaptophysin, Neurofilament

Path Presenter



GANGLIONEUROMA

MORPHOLOGY

- **Ganglion cells** set in **Schwannian stroma**
- Peripheral neuroblastic tumors derive from the **sympathetic nervous system**, often in posterior mediastinum, no neuroblastoma

OTHER HIGH YIELD POINTS

- Most mature, benign. IHC: **Schwann cells (+) S100, Ganglion cells (+) Synaptophysin, neurofilament**

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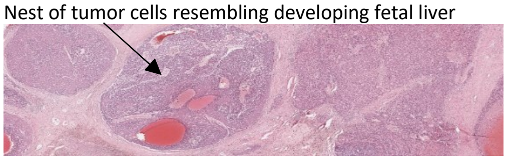
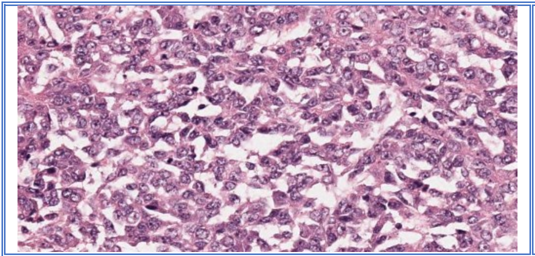
Nest of tumor cells resembling developing fetal liver



HEPATOBLASTOMA

MORPHOLOGY

- Thin **trabeculae or nests** of small to medium sized cells resembling hepatocytes of the **developing fetal liver**
- A variety of epithelial (e.g., fetal and embryonal) and mesenchymal types (teratoid) recapitulating hepatic ontogenesis



OTHER HIGH YIELD POINTS

- **Most common liver tumor in children**
- Gross: Single or multinodular tumor with well-defined boundaries
- Malignant, associated with Beck-Wiedemann
- Frequent b-catenin mutations

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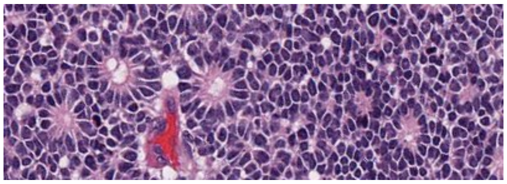
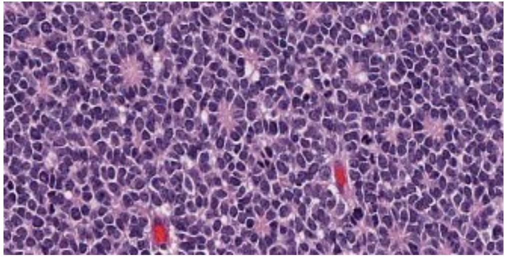
Flexner – Wintersteiner rosettes: Central lumen



Homer Wright rosettes: lack of central lumen



RETINOBLASTOMA

MORPHOLOGY

- Sheets of **numerous small uniform round cells** with **nuclear molding**
- **Flexner-Wintersteiner rosettes:** Most common, central lumen with basally located nuclei, feature of retinal differentiation.
- **Homer-Wright rosettes:** Less common, lack of central lumen, represent neuroblastic differentiation
- **Fleurettes:** Tumor cells arranged side by side with central lumen, represents photoreceptor differentiation

OTHER HIGH YIELD POINTS

- Most frequent intraocular tumor in children,
- Bilateral in 33%; frequently detected younger than 2 years old; 5% have familial antecedents

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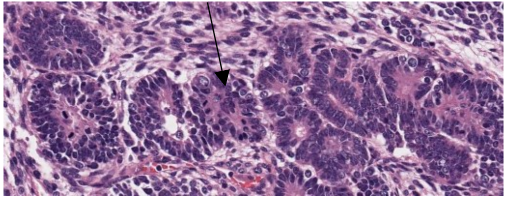
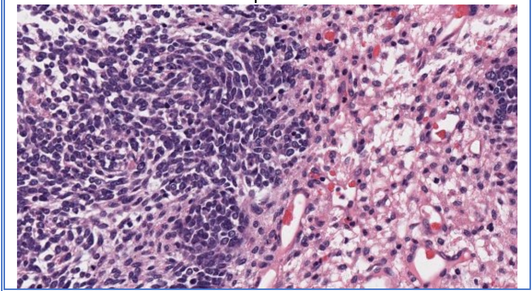
PEDIATRIC KIDNEY TUMORS

Primitive epithelial tubules



Blastemal and stromal components



WILMS TUMOR(NEPHROBLASTOMA)

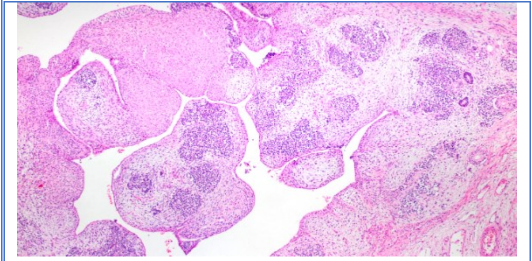
MORPHOLOGY

- 3 key elements**: Primitive epithelial tubules**; **blastema sheets** of small high N:C ratio cells; and **stroma**

OTHER HIGH YIELD POINTS

- Malignant tumor originating in kidney
- **Anaplasia:** Presence of enlarged, atypical, tripolar or multipolar mitotic figures, marked nuclear enlargement and hyperchromasia. All 3 features have to be present
- **Diffuse anaplasia**: non-localized anaplasia; focal anaplasia with marked nuclear unrest in the remaining tumor; anaplasia beyond the tumor capsule; anaplastic cells in intrarenal or extrarenal vessels, renal sinus, extracapsular sites, metastatic deposits or anaplasia in a biopsy
- IHC: **Epithelium**: (+) WT-1, CK; **Blastema** (+) WT-1, Desmin; **Stroma**: weak WT-1, (plus heterologous elements)

Link



CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

MORPHOLOGY

- Well-defined **multilocular cysts** lined by flattened cuboidal epithelium with septa containing **blastema**, **embryonal stroma** or epithelium elements

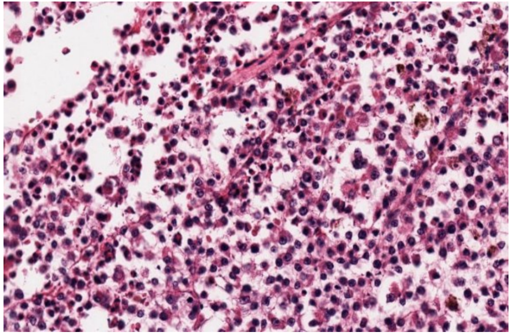
OTHER HIGH YIELD POINTS

- Benign and present as abdominal mass in the first 2 years of life

Path Presenter

16. PEDIATRIC PATHOLOGY

Nested growth with dividing collagenous bands



CLEAR CELL SARCOMA

MORPHOLOGY

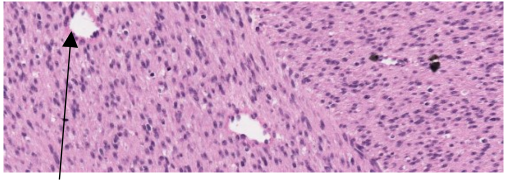
- **Monotonous ovoid to spindle cells** with nuclei that have **conspicuous nucleoli**, and **clear cytoplasm** and arranged in **fascicles** and **nests**
- Cells may also have **melanin pigment** (often focal)
- **Collagen separates nests** and is either sclerotic/dense or delicate
- Scattered **multinucleated giant cells** with **peripherally located nuclei** characteristic → "**wreath cells**"

OTHER HIGH YIELD POINTS

- Malignant, typically, young adults seen in young adults
- **IHC**: **positive** for **all melanocytic markers**
- **Molecular**: **EWSR1-ATF1 → t(12;22)**

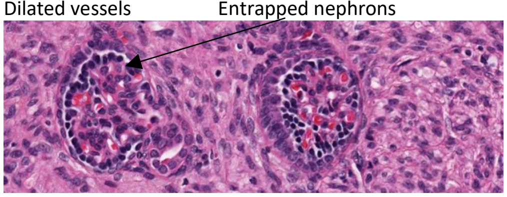
Path Presenter

Fascicles of spindle cells with low mitotic activity

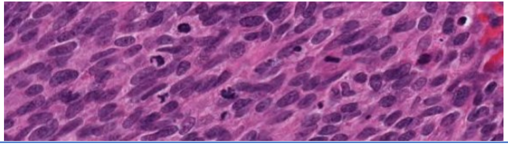


Dilated vessels

Entrapped nephrons



Cellular variant with high mitotic activity



MESOBLASTIC NEPHROMA

MORPHOLOGY

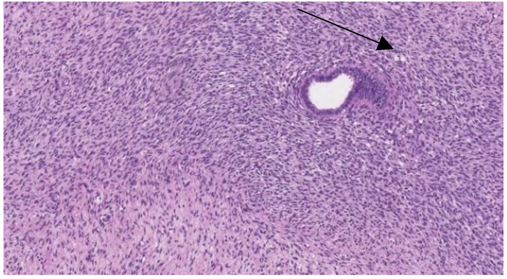
- **Unencapsulated**
- Intermingling **fascicles of spindle cells** with **low mitotic activity**
- **Collagen deposition** can be seen, entrapped nephrons can be present
- Often have **prominent dilated, thin - walled vascular spaces**
- Tumor-kidney border is irregular with **finger-like protrusions** of the tumor into the renal parenchyma

OTHER HIGH YIELD POINTS

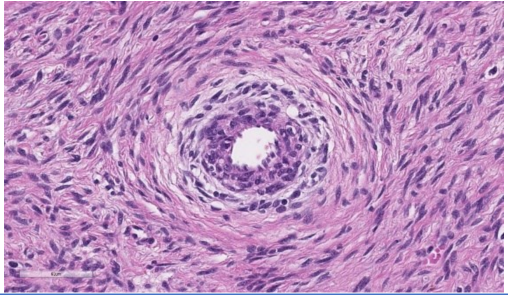
- **Infrequent congenital tumor**, generally benign affecting newborns
- **Three morphologic types:** classic, cellular and mixed.
- **Cellular variant is most frequent:** Comprises of high cellularity of plump cells with vesicular nuclei, moderate amount of cytoplasm, sheet-like growth pattern and a high mitotic
- IHC: CD34(+)

Path Presenter

Alternating cellularity



Onion skin cuffing around entrapped tubules



METANEPHRIC STROMAL TUMOR

MORPHOLOGY

- **Well-circumscribed** and unencapsulated tumor composed of **spindled cells**
- The **tumor - kidney interface** is **clearly demarcated** with only subtle infiltration
- **Nodular appearance**, due to alternating cellularity of spindle cells
- **"Onion skin" cuffing** around entrapped tubules
- **Vascular changes** like angiodysplasia of entrapped arterioles and juxtaglomerular cell hyperplasia can be present

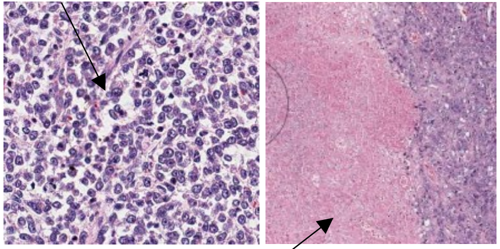
OTHER HIGH YIELD POINTS

- Rare, benign, **stromal tumor** which requires **no further treatment**
- Predominantly affects **children**
- **IHC**: Positive for vimentin, focally positive CD34; negative for WT1, Desmin and SMA
- **Molecular**: BRAF V600E mutation

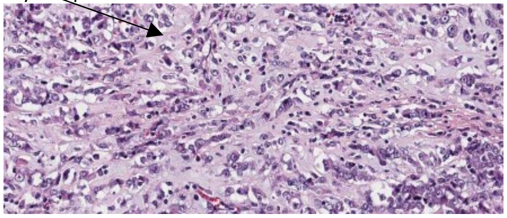
Path Presenter

16. PEDIATRIC PATHOLOGY

Poorly cohesive infiltrative sheets, solid growth



Myxoid pattern Prominent necrosis



RHABDOID TUMOR OF KIDNEY

MORPHOLOGY

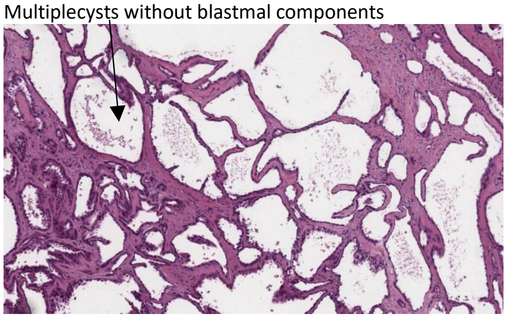
- **Poorly cohesive infiltrative sheets** of tumor with abundant necrosis
- Different patterns: Solid, sclerosing, epithelioid, spindled, cystic, vascular, or myxoid
- **Neoplastic cells** have pink cytoplasm with eccentric nuclei due to intracytoplasmic inclusions of eosinophilic hyaline globules

OTHER HIGH YIELD POINTS

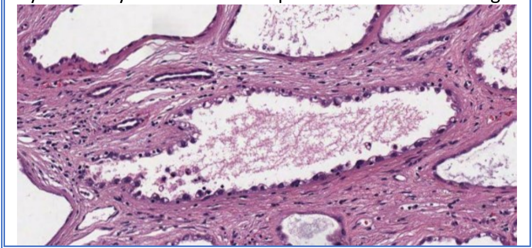
- **Uncommon** but majority diagnosed by age 3; males slightly more common
- Presents as abdominal mass, hypercalcemia, fever, hematuria, and early metastasis
- Very aggressive (80% mortality) and 25% survival at 5-years
- **IHC**: positive for cytokeratin, antichymotrypsin, vimentin; **loss of INI1/SNF5**
- **Molecular:** Mutations in SNF5/INI1

Path Presenter

Multiplecysts without blastmal components



Cyst lined by flat to cuboidal epithelium with hobnailing



CYSTIC NEPHROMA

MORPHOLOGY

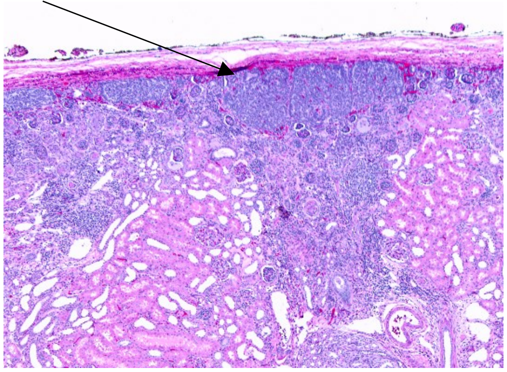
- Multicystic with variably sized simple cysts lacking immature nephrogenic elements, solid areas and cytologic atypia
- Cyst lining epithelium is flattened to cuboidal, with frequent hob nailing
- No epithelial complexity (branching glands, papillary projection, cribriforming)
- Partial or complete fibrous pseudo capsule often containing entrapped tubules and glomeruli; some tumors intermingle with normal parenchyma
- Absence of blastemal element. Multilocular cysts of varying sizes with thin septa, lining by tubular epithelium

OTHER HIGH YIELD POINTS

- Rare, benign. Commonly seen in 2-4 years old, boys are more affected
- Surgical intervention is effective

Path Presenter

Embryonal cells



NEPHROGENIC RESTS

MORPHOLOGY

- Abnormally **persistent foci of embryonal cells**: small primitive blue cells
- **Kidneys** are **developmentally normal**
- Usually occur along the perimeter of a mature lobe(perilobar), within the lobe itself (intralobar) or combined

OTHER HIGH YIELD POINTS

- Represent **precursors of nephroblastoma**
- Associated with certain syndromes carrying the risk of nephroblastoma
- Share many of the same chromosomal defects of Wilms's tumor

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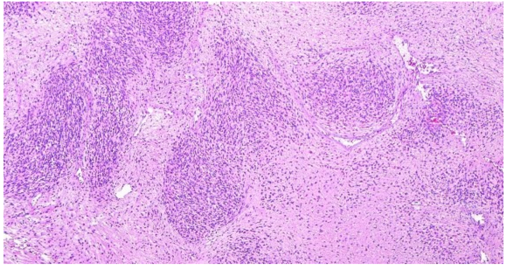
Embryonal RMS: Hypo & hypercellular areas



Round cells with deeply eosinophilic cytoplasm

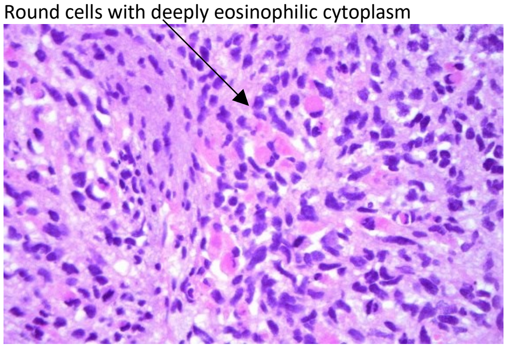
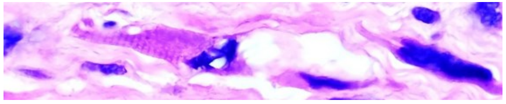
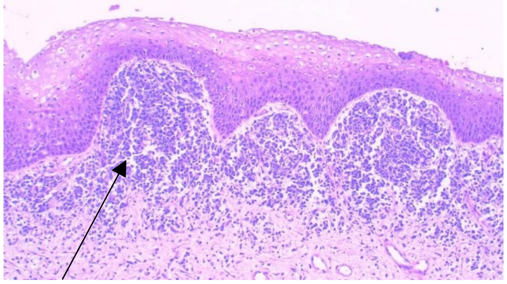


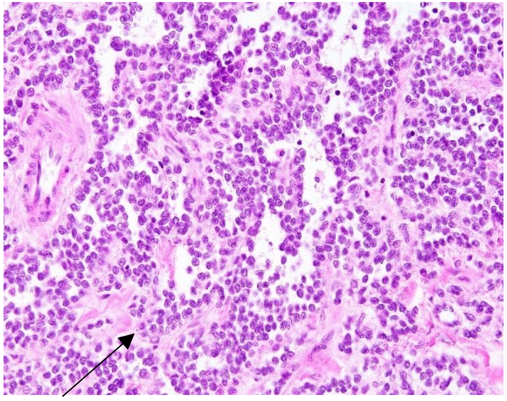
Image courtesy: Brendan Dickson, MD



Strap cell with cross striations, image courtesy: Aung Phyo, MD



Cambium layer in Botyroid variant, image courtesy: Jose Candido, MD



Alveolar RMS with hobnailing alveolar pattern

RHABDOMYOSARCOMA

MORPHOLOGY

EMBRYONAL RHABDOMYOSARCOMA:

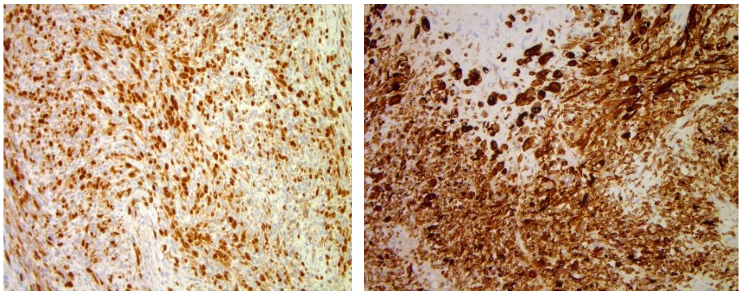
- **Primitive mesenchymal cells** that show variable degrees of **skeletal muscle** differentiation.
- Often contain both **hypocellular and hypercellular areas** with a loose, myxoid stroma
- Sheets of small, stellate, spindled or round cells with scant or deeply **eosinophilic cytoplasm** and eccentric, small oval nuclei with a light chromatin pattern and inconspicuous nucleoli
- May have cells with elongated tails of cytoplasm **(tadpole cells)**
- **Botryoid variant** Shows a cambium layer: a hypercellular zone immediately beneath the epithelial surface

ALVEOLAR RHABDOMYOSARCOMA:

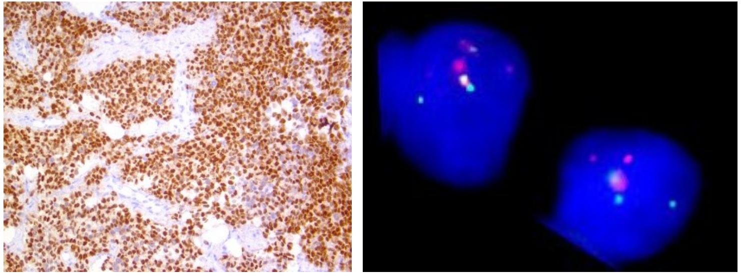
- Larger, more rounded undifferentiated cells with only occasional rhabdomyoblasts
- Often arranged in an **alveolar pattern**
- Cells adhere to the periphery of the alveoli creating a **Hobnail or tombstone appearance**
- Distinctively strong and diffuse Myogenin positivity
- **Multinucleated** giant cell forms may be seen
- Occasional rhabdomyoblasts seen in few cases

OTHER HIGH YIELD POINTS

- IHC: Positive staining with Desmin, MyoD1, Myogenin
- **Molecular**: t(2;13) PAX3-FOXO1 or t(1;13) PAX7-FOXO1 translocations

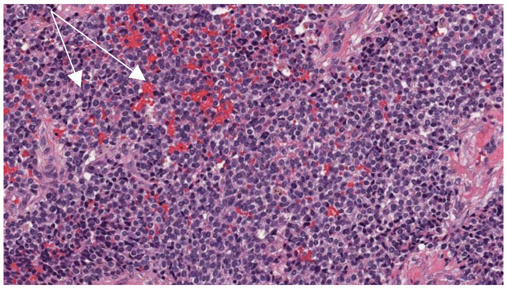


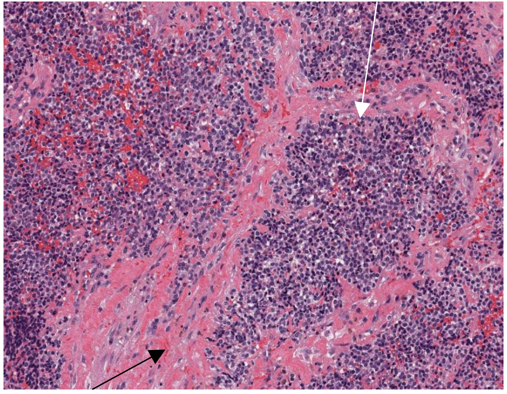
Embryonal Rhabdomyosarcoma: Myogenin and Desmin

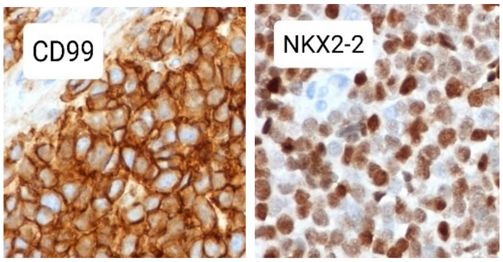


Alveolar RMS: Myogenin and FOXO break apart FISH (image courtesy: Jake Bledsoe, MD)

Path Presenter







IHC images courtesy: Raul Perret, MD, MSc @kells108

EWING SARCOMA

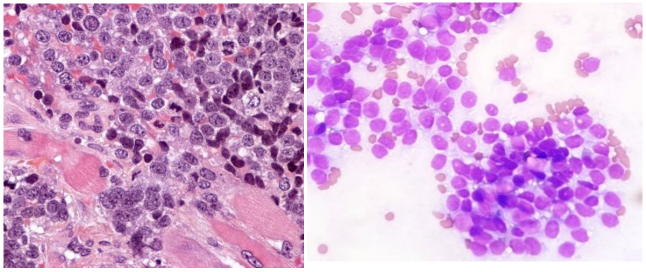
MORPHOLOGY

- **Uniform round blue** cells with **finely granular chromatin** and **occasional nucleoli**, and **vacuolated cytoplasm**
- **Sheet-like or lobular growth** pattern; **rosettes** may be seen
- **Inconspicuous mitosis**
- **Necrosis** and **apoptosis** are typical and scattered about

OTHER HIGH YIELD POINTS

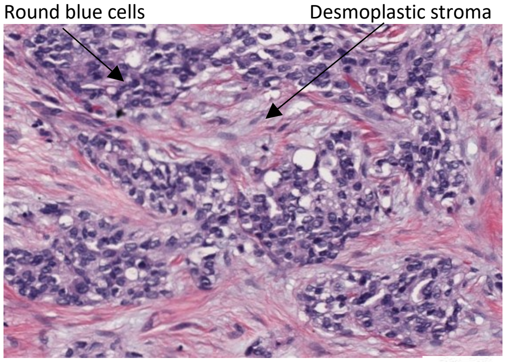
- **Young adults**, **painful mass**, **fever**, **weight loss**, **pathologic fracture**
- **Most** common **affected** bones are the **femur**, **tibia**, and **humerus**
- **Radiographic**: "**moth-eaten**" appearance of bone
- **Metastasis** occurs early → typically to the lungs
- **Favorable prognosis**: **age (<10)**, **location** (non-pelvic bone), <8 cm size
- **IHC**: **positive** for **CD99**, **vimentin**, and **FLI**1
- Molecular: Several translocations
  - **Most common (95%): EWSR1-FLI1** → t(11;22)(q24;q12)
  - Type 1 fusion better prognosis: EWSR1 exons 1-7 fuse to FLI1 exons 6-9
  - Less common: EWSR1-ERG → t(21;22)(q22;q12)
  - Alternatives, less than 5% of cases:
    - EWSR1-E1AF → t(17;22)(q12;q12)
    - EWSR1-PATZ1 → t(1;22)(p36;q12)
    - EWSR1-ETV1 → t(7;22)(p22;q12)
    - EWSR1-FEV → t(2;22)(q33;q12)

Path Presenter


Muscle infiltration

"Round blue cells" on Cytologic Prep

Images courtesy: Raul Perret, MD, MSc @kells108



Path Presenter

DESMOPLASTIC SMALL ROUND CELL TUMOR

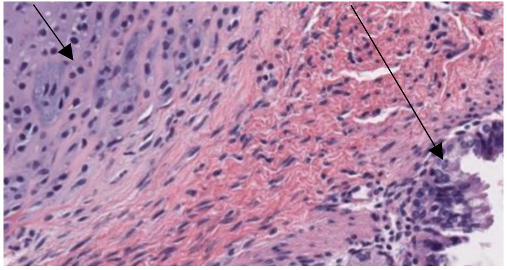
MORPHOLOGY

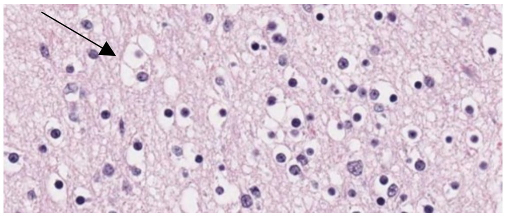
- Primitive **round blue cells** arranged in **sheets**, **nests**, or **trabeculae**
- Background **desmoplastic stroma**
- Tumor cells **may have rhabdoid**, **clear cytoplasm**, or **spindled morphology**
- **Rosette-like structures**
- Variable **necrosis**

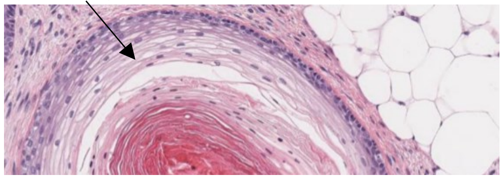
OTHER HIGH YIELD POINTS

- Most common in **children** and **young adults** with a **male predilection**
- Tumors are usually **large** and are **palpable** upon exam
- Has a **poor prognosis**, nearly all patients die within 2 years
- **IHC**: Positive for Cam5.2, CKAE1/AE3, desmin (dot-like), WT1, and NSE; variably positivity for CD99, synaptophysin, chromogranin, and S100
- **Molecular**: **EWSR1-WT1 fusion**→ **t(11;22)(q13;q12)**

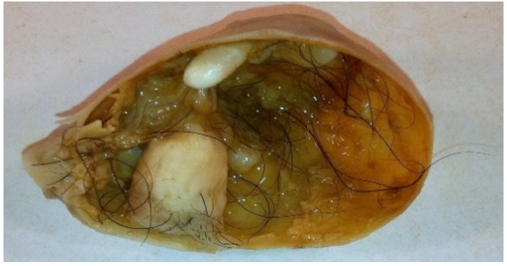
16. PEDIATRIC PATHOLOGY







Gross specimen



Courtesy of Dr. Ed Uthman

Path Presenter

TERATOMA

MORPHOLOGY

- Composed of tissues from 2-3 germ layers and are often **unilateral**
- **Common elements:** skin (with adnexal structures), cartilage, gastrointestinal epithelium, and neural tissue
- **Mature:** exclusively mature tissue and almost always cystic
  - Contains **teeth** in 33% of cases
  - May have **Rokitansky protuberance**: solid nodule that projects into lumen and contains adipose, bone, or teeth
  - Benign unless a secondary somatic malignancy develops (usually carcinoma such as SCC or PTC)
- **Immature:** contains **mixture of mature** and **immature elements**
  - Usually are encapsulated and solid
  - **Neuroepithelial rosettes** and tubules
  - Glial tissue with mitoses
  - Immature cartilage, muscle, bone, or glandular structures
- **Struma ovarii:** thyroid tissue is sole tissue or predominant tissue
  - Most often resembles a follicular adenoma
  - **Rare** in pediatric patients

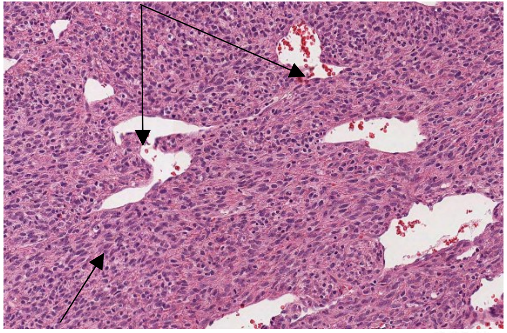
OTHER HIGH YIELD POINTS

- Can arise essentially anywhere but may present as an abdominal mass or ovarian rupture or torsion
- Laboratory tests: low-level AFP
- Grade based on amount of immature neuroepithelium

GRADE	AMOUNT OF IMMATURE NEURAL TISSUE
1	Rare foci (<1) in a low power field in any slide
2	2-3 low power fields in any slide
3	4 or more low power fields in any slide

ECTODERMAL	ENDODERMAL	MESODERMAL
Teeth	Thyroid tissue	Bone
Neural tissue	Respiratory structures	Cartilage
Epidermis	Gastrointestinal structures	Smooth muscle
Skin adnexa		Striated muscle
		Adipose

SOFT TISSUE



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INFANTILE FIBROSARCOMA

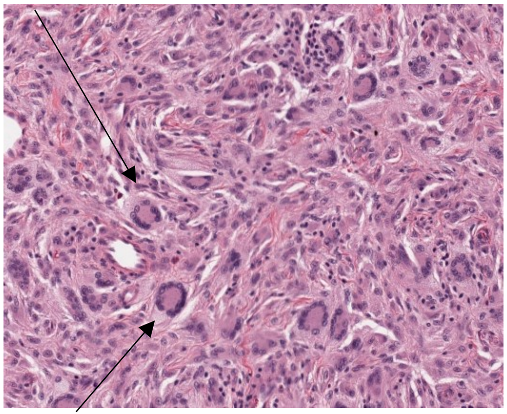
MORPHOLOGY

- Infiltrative **monomorphic spindle cells** in **sheets** or **sweeping fascicles**
- May have a **primitive** (**round cell**) **component** and **brisk mitotic activity**
- Hemorrhage and necrotic foci common
- Hemangiopericytoma-like vessels or myxoid change, or necrosis

OTHER HIGH YIELD POINTS

- **Majority** of cases **occur within 1st year** of life, **slight male** predilection, **nearly 50%** of cases are **congenital**
- Clinically presents as a **rapidly growing solitary mass** +/- skin changes
- Often in distal extremities (most common), head and neck, or trunk
- **Favorable prognosis** (mortality rare) but **recurrence in 50%** of cases
- IHC: **PanTRK positivity** (cytoplasmic)
- **Molecular**: ***ETV6-NTRK3*** → t(12;15)(p13;q25)

16. PEDIATRIC PATHOLOGY



JUVENILE XANTHOGRANULOMA

MORPHOLOGY

- Dense dermal **histiocytic infiltrate** and does not involve epidermis
- Overlying **epidermis is attenuated** and has **long rete ridge**s
- **Touton giant cells** with "**wreath-like**" nuclei
- Rare mitotic figures

OTHER HIGH YIELD POINTS

- **Benign** and usually seen in ages **under 1 year**
- Common in **males** and located in head, neck, trunk, or extremities
- Associated with **Neurofibromatosis type 1**, Niemann-pick, and urticaria pigmentosa
- Mainly clinical diagnosis, sometimes a biopsy analysis is required
- **IHC**: Positive for CD68; negative for S100 and CD1a

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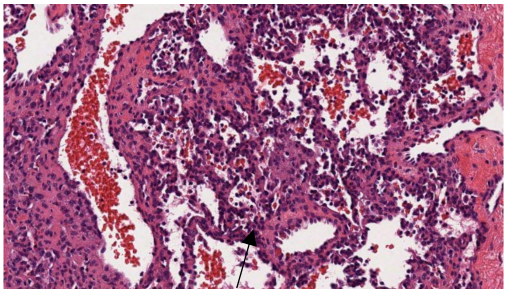


INFANTILE HEMANGIOMA

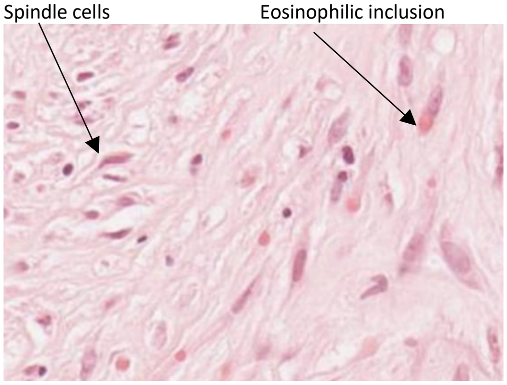
MORPHOLOGY

- Tumor composed of **small or large caliber thin-walled** blood **vessels**
- Single layer of non-atypical endothelial cells

OTHER HIGH YIELD POINTS

- Onset during **infancy**, **rapid growth** and has **spontaneous involution**
- **IHC**: Unique expression of **GLUT1**(not in other hemangiomas)
- Associated with PHACE and LUMBAR syndrome

Path Presenter



INCLUSION BODY FIBROMATOSIS

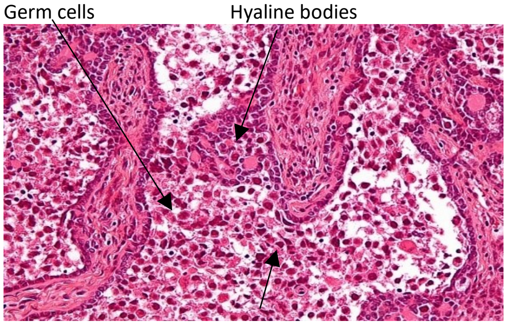
MORPHOLOGY

- Intradermal **proliferation** of **fibroblasts/myofibroblastic spindle cells** arranged in **fascicles**, **whorls**, or **sheets**
- Perinuclear, **intracytoplasmic eosinophilic inclusion**
- No necrosis or mitosis

OTHER HIGH YIELD POINTS

- **Rare** and typically seen in the **first 3 years of life**, no sex predilection
- **Painless mass** that presents on **dorsal aspect of fingers** and toes
- IHC: Positive for SMA and calponin

Path Presenter



Courtesy of Dr. Michael Bonert, MD

GONADOBLASTOMA

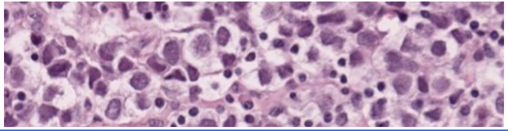
MORPHOLOGY

- Germ cells are round and large and have vesicular nuclei, conspicuous nucleoli, and abundant cytoplasm
- Immature Sertoli and granulosa cells are scattered about and surround pink hyaline bodies
- More than 50% have a dysgerminoma component

OTHER HIGH YIELD POINTS

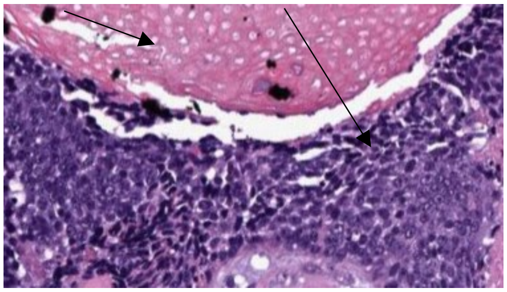
- Very rare tumor and is predominantly in young women with gonadal dysgenesis or pseudohermaphrodites
- Presents clinically as primary amenorrhea, genitalia abnormalities, virilization, or as a tumor

Dysgerminoma



- Pure tumors are benign and considered an in situ component if malignant germ cell component is present

Path Presenter



PILOMATRICOMA

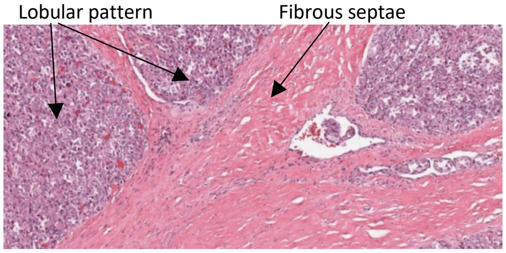
MORPHOLOGY

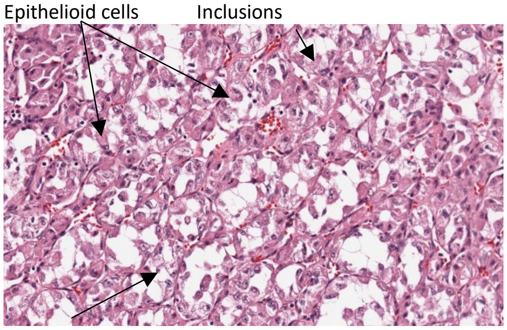
- Well-circumscribed with mixture of basaloid and ghost cells
- Dystrophic calcification is frequently seen
- Foreign-body giant cell reaction surrounding tumor is common

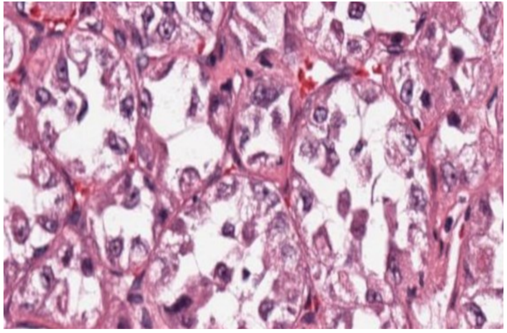
OTHER HIGH YIELD POINTS

- Most common to occur in head and neck and is slow growing

Path Presenter







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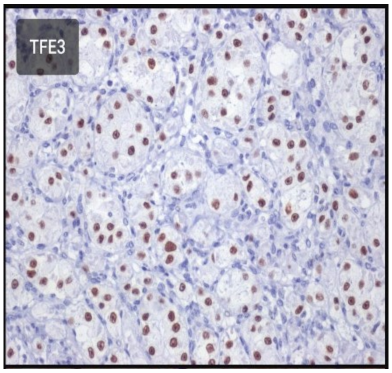
ALVEOLAR SOFT PART SARCOMA

MORPHOLOGY

- Large, **uniform epithelioid cells** with **round nuclei** and **conspicuous nucleoli**, and **abundant** granular **eosinophilic cytoplasm**
- **Compartmentalization → lobules**, nests with **fibrocollagenous septa**
- Rod to rhomboid-shaped intracytoplasmic inclusions
- **Pseudoalveolar pattern → tumoral nests** with an **empty central portion** due to **absence of cohesion** and degeneration
- **Necrosis** is **uncommon** and mitotic activity is low

OTHER HIGH YIELD POINTS

- **Rare** and predominantly seen in **infants** and **young adults** with a **female predominance**; **slow-growing mass** in **anterior thigh/buttocks**
- **Metastasis present in 50%** of patients at diagnosis
- **Poor prognosis** → present with metastasis to lung and brain
- Most important **favorable factors**:
    - Small size (<5 cm), young age at diagnosis (<10), no metastasis
- **IHC**: **Positive** for **TFE3**; variable S100 and desmin
- **Special stains**: **PAS** highlights intracytoplasmic inclusions
- **Molecular**: **der(17)t(X;17)(p11.2;q25)** → ASPSCR1 (ASPL)-TFE3 fusion



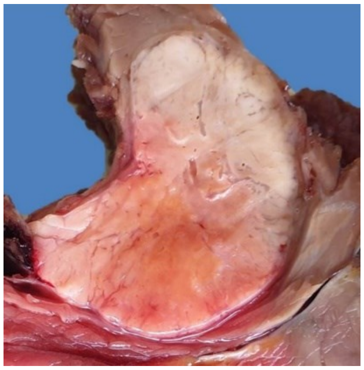
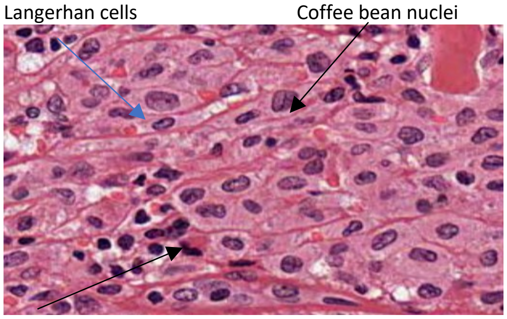


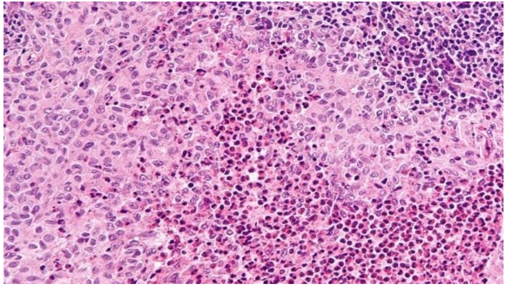
Image Credit: Raul Perret, MD, MSc @kells108

16. PEDIATRIC PATHOLOGY

Langerhan cells Coffee bean nuclei

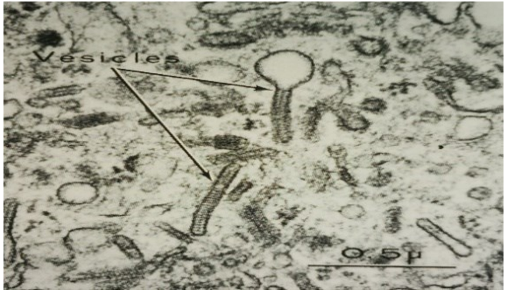


Eosinophils Langerhans cells



Courtesy of Dr. Michael Bonert

Electron Microscopy of Birbeck Granules



Courtesy of Dr. Philip Kane and Dr. Yale Rosen

LANGERHAN CELL HISTOCYTOSIS

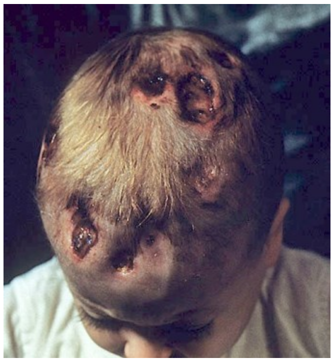
MORPHOLOGY

- **Langerhans cells**: folded “coffee bean nuclei”, open chromatin, and granular pale eosinophilic cytoplasm
- **Eosinophils** are scattered about

OTHER HIGH YIELD POINTS

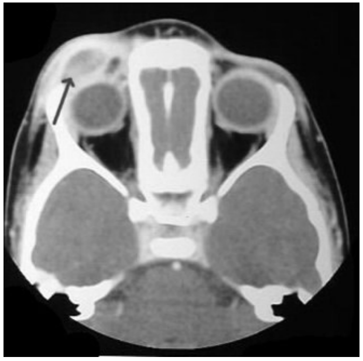
- **Clonal neoplasm** seen within first 3 decades of life, male predominance
- Can involve the skin, skull, axial skeleton, lungs, lymph nodes
- **Single site:** Eosinophilic granuloma
- **Hand-Schuller-Christian disease:**
  - ➢ Multiple organ involvement by neoplasm, **exophthalmos**, and **diabetes insipidus**
- **Letterer-Siwe Disease:**
  - ➢ **Aggressive** and disseminated disease and often death within 1 year
- IHC:**(+)S100, CD1a, Langerin (CD207)**; (+/-), CD68
- **Molecular**: BRAF V600E mutation
- **Electron Microscopy**: Birbeck granules (tennis racket shaped)

Hand-Schuller-Christian Disease



Courtesy of Dr. Thomas Habif

LCH involving the Orbit



Courtesy of the University of Cincinnati

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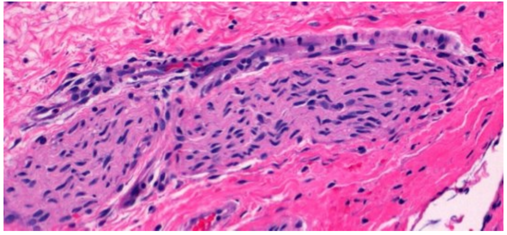
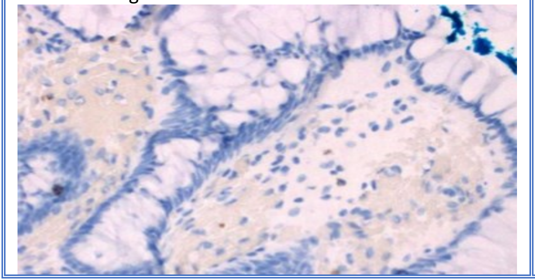
NON-NEOPLASTIC PEDIATRIC PATHOLOGY

Neural hypertrophy



No nerve twigs on calretinin IHC



HIRSCHSPRUNG DISEASE

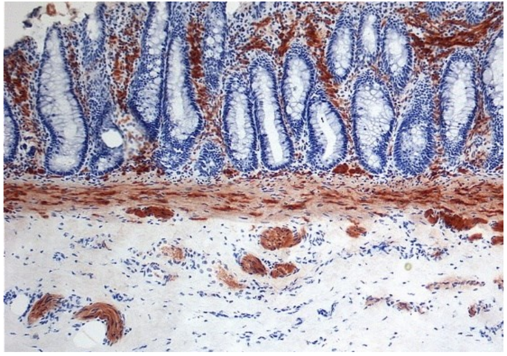
MORPHOLOGY

- **No ganglion cells** in **myenteric** or **submucosal plexuses**
- **Hypertrophied nerve fibers** of myenteric and submucosal plexuses
  - ➢ **Neural hypertrophy**: submucosal nerves **> 40 µm**

OTHER HIGH YIELD POINTS

- **Suction biopsy should be >2 cm above dentate line** to avoid physiologic area of fewer ganglion cells
- Suction biopsy should be **>3mm in diameter** and at **least 1/3 of the thickness** should be submucosa
- If no ganglion cells, order additional ribbons and levels along with calretinin
  - ➢ Do not want to take out a colon that doesn’t need to come out
  - ➢ **Caution**: Ganglion cells in infants have less Nissl substance and have higher N/C ratios than adult ganglion cells
- **IHC/Special stains:** Nerve twigs are negative for calretinin; No ganglion cells are present on calretinin staining; Positive abnormal acetylcholinesterase staining

Abnormal Acetylcholinesterase Staining



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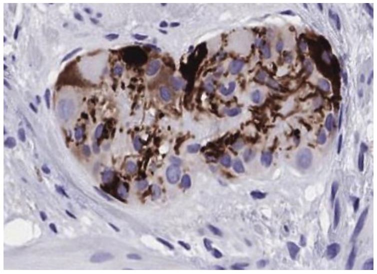
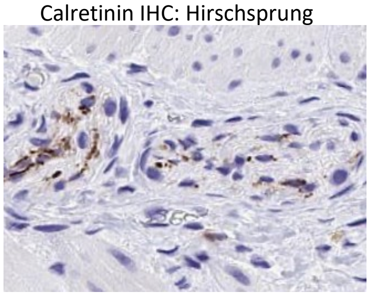
- **Pathogenesis: Failure of neuroblasts to migrate and/or differentiate in distal bowel**
- Molecular: RET (~80% of long segment disease type)

Calretinin IHC: Normal Colon

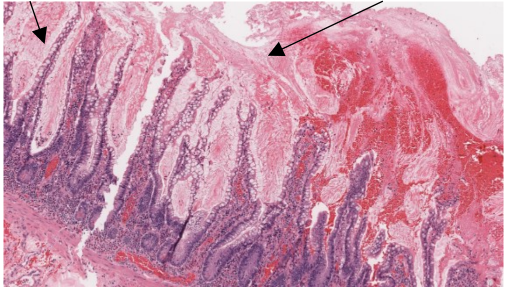


Calretinin IHC: Hirschsprung

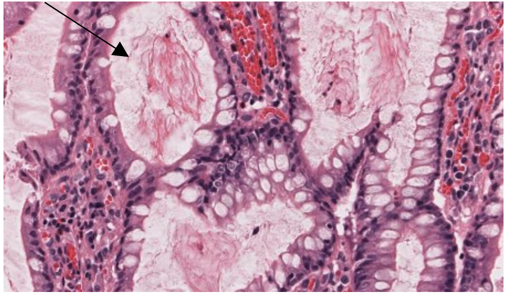


Tall villi

Eosinophilic mucin

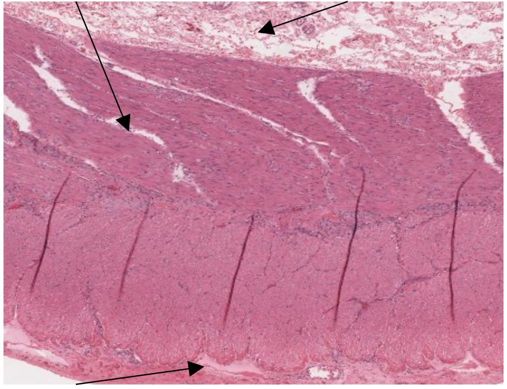


Inspissated mucin



Muscularis propria thickening

Edema



Serosal congestion

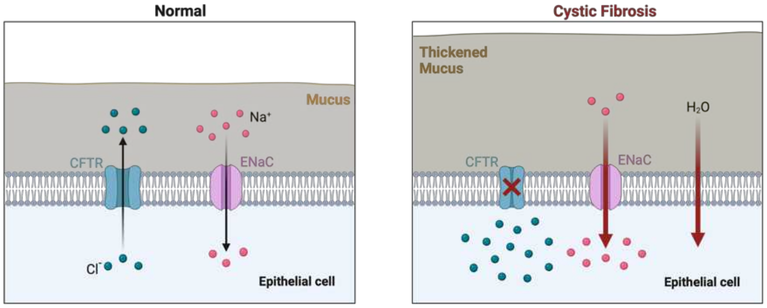
CYSTIC FIBROSIS

MORPHOLOGY

- **Dilated glands** with **inspissated**, eosinophilic **mucin**
- Tall villi that are lined by **hypertrophic goblet cells**
- May have **fibrosing colonopathy**
    - ➢ Muscularis propria thickening and fibrosis
    - ➢ Fibrosis of submucosa
    - ➢ Increased number of mast cells in submucosa and muscularis propria

OTHER HIGH YIELD POINTS

- Clinically may present as **meconium ileus** or **pancreatic insufficiency**
- Later in life, present with chronic and recurrent pulmonary infections, inflammation, exocrine pancreatic insufficiency, and male infertility
- **Genetics:**
    - ➢ **Autosomal recessive** inheritance
    - ➢ Mutations in the cystic fibrosis transmembrane conductance regulator (**CFTR**) **gene** at **7q31.2**
    - ➢ **Most common** mutation: **CFTR ΔF508**
    - ➢ **Dramatically decreased chloride secretion** → causes marked **increase in sodium absorption** → **dehydrates mucin** in lumen
- Laboratory tests:
    - ➢ **Pilocarpine iontophoresis:** elevated sweat chloride → **positive**
    - ➢ Genetic **mutational analysis**



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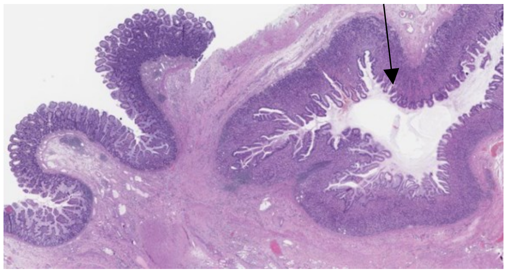
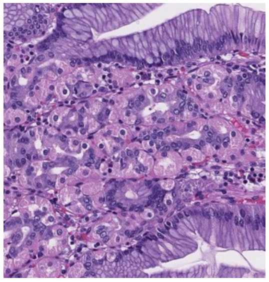
CFTR 7q31.2

16. PEDIATRIC PATHOLOGY

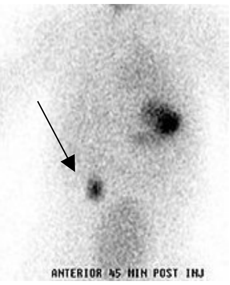
Lumenal mucosa True diverticulum



Gastric-type mucosa



Technetium 99m



Technetium 99m scan courtesy of Dr. Jason R. Young

MECKELS DIVERTICULUM

MORPHOLOGY

- **True** intestinal **diverticulum**
- Contains all normal layers of the gastrointestinal wall
- Can contain either ectopic gastric or pancreatic parenchyma

OTHER HIGH YIELD POINTS

- Most common congenital gastrointestinal malformation (~2% population)
- Can be seen at **any age** as it is **largely asymptomatic**
  - **Males** to female ratio is 3:1
  - If **symptomatic:** right lower quadrant **(RLQ) pain**
- **Children** may present with **gastrointestinal bleeding**
  - Most common cause of gastrointestinal bleeding in children
- **Cause**: persistence of the **congenital omphalomesenteric (vitelline) duct** which cause ileal outpouching
- **Diagnostic test: Technetium 99m Pertechnetate scan**
  - Most specific test for this: Pertechnetate accumulates in the ectopic mucosa ("Hot" due to increased uptake)

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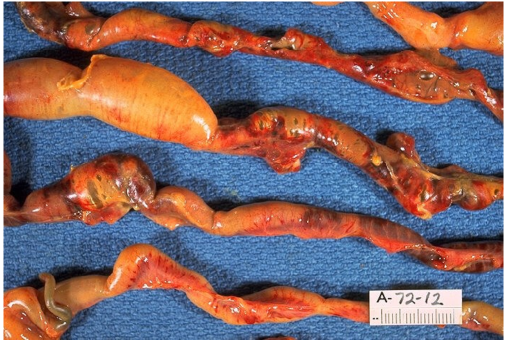
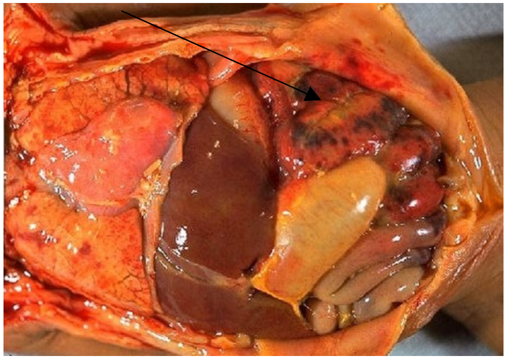
Gross image during autopsy



Bowel discoloration, purulence



Courtesy of Dr. Edwin P. Ewing, Jr.

NECROTIZING ENTEROCOLITIS

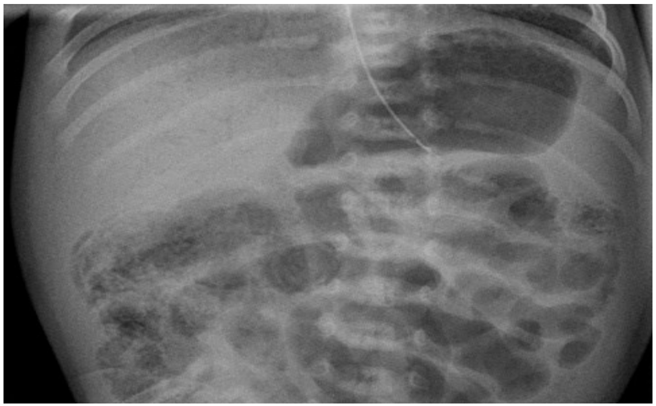
MORPHOLOGY

- **Coagulative necrosis** and **hemorrhagic necrosis** of the small bowel and proximal colon
- **Few inflammatory** cells are seen

OTHER HIGH YIELD POINTS

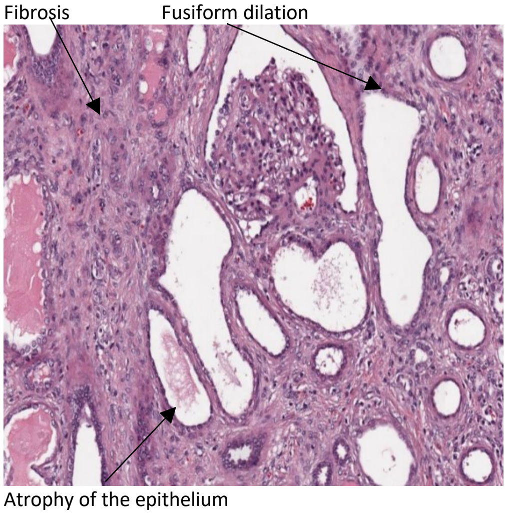
- Usually seen in **premature infants** during first 3 weeks
- Patients are often **very ill** and may have **diarrhea**, **bloody stools**, **lethargy**, **fever**, **feeding intolerance**
- Etiology is uncertain but believed to be due to gut **microbiome imbalance**
- **Death is due to perforation** and subsequent sepsis; mortality up to 40%
- **Radiographic findings:** Pneumatosis intestinalis

Pneumatosis Intestinalis



Radiograph courtesy of Dr. Hellerhoff

16. PEDIATRIC PATHOLOGY



AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

MORPHOLOGY

- **Cortical** and **medullary collecting ducts** with **fusiform dilation**
- **Nephrons** are **normal** and lack dysgenic features
- **Young children**: Interstitial fibrosis and tubular atrophy
- **Older children:** proximal tubule ectasia, medullary cysts, and tubulointerstitial scarring
- Distinctive radiating pattern of cysts in cortex and medulla lined by cuboidal cells

OTHER HIGH YIELD POINTS

- Rare and **mortality is 30%** in the first year of life
- Inheritance: Autosomal recessive
- Mutation: **PKHD1 mutations**
- **Imaging:** large, echogenic kidneys

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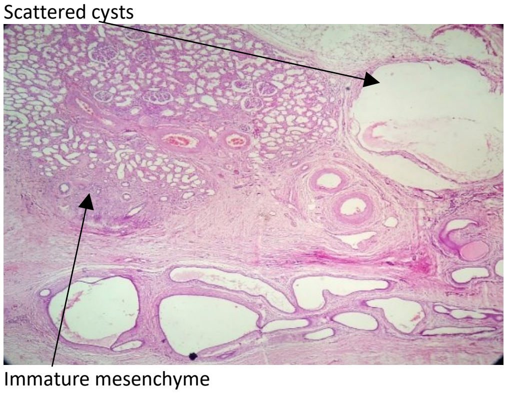

RENAL DYSPLASIA

MORPHOLOGY

- **Immature** and **reduced** number of **nephrons**
- Scattered **cysts**
- **Collarettes** of **smooth muscle**
- **Immature mesenchyme** and disorganized tubules

OTHER HIGH YIELD POINTS

- If **unilateral, prognosis** is **good**
- Due to **abnormal metanephric differentiation**(maldeveloped), usually sporadic
- Usually has associated ureteral abnormality

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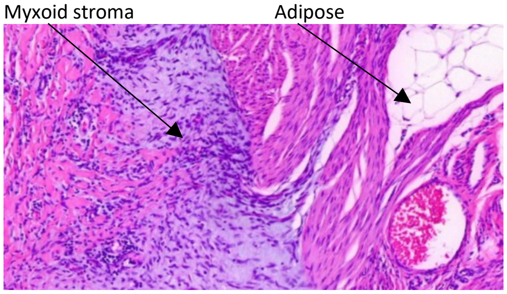

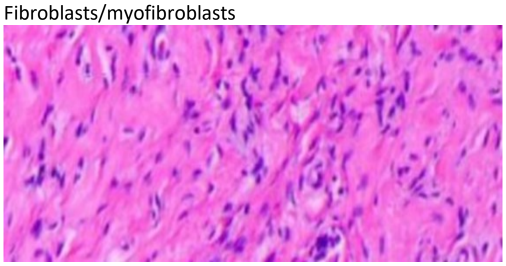

FIBROUS HAMARTOMA OF INFANCY

MORPHOLOGY

- **Fibroblasts/myofibroblasts** in sheets and fascicles
- Immature mesenchymal cells in nests with a surrounding myxoid stroma
- Mature adipose tissue

OTHER HIGH YIELD POINTS

- Benign superficial fibrous lesion occurring during first 2 years of life
- Most common to see in males and has no known syndromic association
- Immunohistochemistry:
    - ➢ **Fibroblastic areas:** positive for SMA
    - ➢ **Myxoid/collagenous areas:** positive for CD34
    - ➢ **Adipose:** positive for S100
- **Molecular**: EGFR exon 20 insertion/duplication

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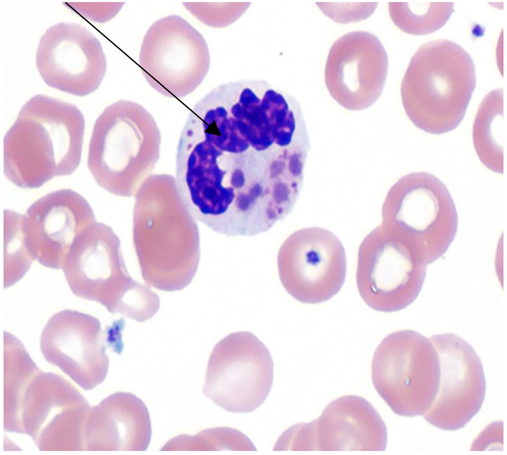

Picture courtesy: University of Michigan

CHEDIAK-HIGASHI SYNDROME

MORPHOLOGY

- Granulocytes with large and often fused **azurophilic granule**s
- Bone marrow precursors have **azurophilic granules**
- **Neutropenia**
- **Hemophagocytosis** in accelerated phase

OTHER HIGH YIELD POINTS

- Presents with **partial oculocutaneous albinism**, **neutropenia** and recurrent **infections**, mild **bleeding** from mucosal surfaces
- Accelerated phase occurs in 80% of individuals and resembles lymphoma
- Autosomal recessive inheritance
- Laboratory tests:
    - **Platelet function: Reduced second wave** of aggregation
    - **Molecular** mutation in LYST or CHS1

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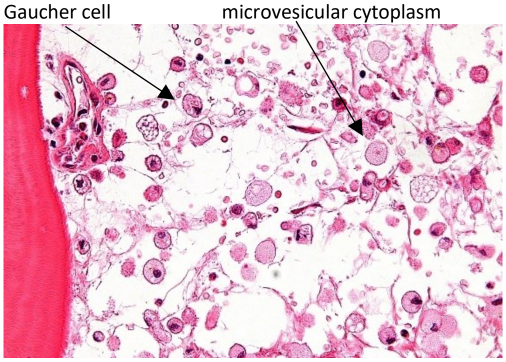
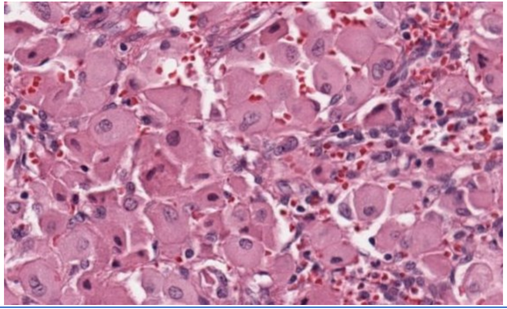


Courtesy of Dr. Michael Bonert



GAUCHERS DISEASE

MORPHOLOGY

- **Histiocytes** with microvesicular "**tissue paper-like**" and/or fibrillary amphophilic cytoplasm

OTHER HIGH YIELD POINTS

- Most common lysosomal glycolipid storage disease due to enzyme deficiency
    - **Lack of Glucocerebrosidase** (Acid β-glucosidase)
    - Causes **accumulation** of **glucosylceremide (glucocerebroside)** in phagocytes
- Present as hepatosplenomegaly, thrombocytopenia, anemia or leukopenia
- **3 major phenotypes:**
    - **Type I**: presence of bone disease, hepatosplenomegaly, anemia and thrombocytopenia, lung; 60% of cases diagnosed before second decade of life
    - **Type II (infantile):** acute neuropathic disease
    - **Type III (juvenile):** chronic neuropathic disease
- **Treatment**: type I and type III can be treated with enzyme replacement
- **Molecular**: mutation in GBA resulting in a c.1226A>G
    - GBA encodes glucocerebrosidase on chromosome 1q21

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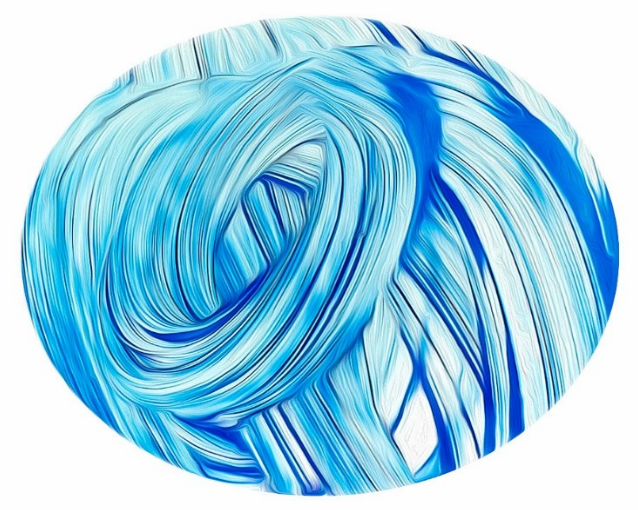


Who knew a “dot under a microscope” might constitute for a Path Art! Image courtesy: Ziad El-Zaatari, MD

CHAPTER 17: FORENSIC PATHOLOGY

Kristy Waite, MD
Terrance Lynn, MD
Akanksha Gupta, MD

17. FORENSIC PATHOLOGY

INTRODUCTION

- Forensic pathology unites medicine, law, and the post-mortem examination of a body
- Forensic autopsies document deaths that belong to **natural, accidental, suicide, homicide, and undetermined** causes of death
- A specially trained pathologist performs such autopsies with a subsequent **board** examination in forensic pathology
- In addition to performing the post-mortem examination, forensic pathologists **testify in court** and **visit the scene** of the body

MEDICOLEGAL DEATH INVESTIGATION SYSTEM

- Each **state has its own system** for a medicolegal death investigation
- Systems can be organized as a **Medical Examiner, Coroner, or Mixed system**
- A **Coroner** is an elected official that is responsible for the medicolegal death investigation
    - Often operate at the county level
    - **Not** required to be physician
    - **Do not perform autopsies**
    - Hire forensic pathologists to perform autopsies
    - **Completes death certificates** with the cause of death and manner of death
- A **Medical Examiner** is a physician who is appointed with the duty of performing a medicolegal death investigation
    - May serve a city, county, region, or at the state level
    - Often are **pathologists**
    - **May perform autopsies**; however, in some systems, the ME is **only in charge of the death investigation** and does not perform autopsies
    - Medical examiner means different things based on location
- A **Forensic Pathologist** is a physician (MD/DO) who has either AP training, AP/CP training, and a fellowship in forensic pathology
    - May or **may not** be board certified
    - **Performs autopsies**, complete autopsy reports, and may **sign death certificates**
    - Can be employed in private practice, military, state, regional, or local governments

CASES REPORTABLE TO THE CORONER/MEDICAL EXAMINER'S OFFICE

- There are variations depending on the jurisdiction
- Common causes include:
    - Sudden and **unexplained** deaths
    - Deaths **within 24 hours** of admission to a healthcare facility
    - Deaths that are related to **unlawful or unnatural** matters:
        - Drug/illicit substance-related deaths
        - Abuse or neglect
        - Self-inflicted injuries
        - Injuries inflicted by another individual
        - Environmental exposure
    - Deaths with **suspicious circumstances**
    - **Infectious**, contagious diseases
    - Deaths resulting from **therapeutic** misadventures or surgical interventions
    - **Occupational** injuries resulting in death
    - Deaths occurring in individuals who are **under the custody** of the state or penal institutions:
        - Prison, state hospitals
    - Deaths of **unidentified individuals**
    - Deaths involving **children**:
        - Suspected or confirmed Abuse or neglect cases
        - Unattended deaths
        - Under state custody
        - Suspicious or unnatural deaths
        - Sudden Unexplained Death of Infant (SUDI)
    - **Decomposed** bodies or skeletal remains
    - **Fetal deaths:**
        - Often if <20 weeks gestation
        - Suspected maternal drug abuse
        - Birthweight of 350 grams
        - Others are defined by state
    - Deaths of individuals under the **care of hospice**

INVESTIGATION OF THE SCENE OF THE DEATH

- Provides a critical portion of the **evidence** that gives circumstance and context of an individual's death
- This could be the location where **events immediately preceding** death occurred, the **place at which death occurred**, or where the body was found
- Not every scene where the body is found is the scene where the death occurred:
    - Body discarded in a wooded area to hide
    - Body tied down at the bottom of the lake
    - Body burned in a woodpile to destroy evidence
- **Scene investigation** occurs in conjunction with the medical examiner/coroner, law enforcement, and even the district attorney's office
- **Photography** of the scene is essential to document the surroundings in which the body was found
    - Including temperature and weather where the body was found
- Thorough **interview** of bystanders/other individuals
    - Individuals **may be re-interviewed** later
- Collection of evidence and creation of a **chain of custody**
    - Evidence is then taken and stored in a secure facility
- The decedent is then **photographed** and evaluated by the medical examiner or coroner
    - Pictures of the **face** (as found)
    - Images of the **entire body** (as found)

  - Photographs of the **back of the body** (as found)
- It is imperative to collect and keep evidence on the body in an appropriate manner to avoid destroying
  - **DNA** from fluids and other sources can **degrade rapidly** (or be contaminated) if mishandled
- Physical examination of body unclad can occur at the site or in a morgue/at the time of autopsy
- Important **documentation** of the body should include:
  - Evaluation of rigor mortis, livor mortis, decomposition changes, insect activity, animal predation, etc.
- If **any medication, drugs, alcohol** (or other items such as a suicide note) are found, documentation is essential

DECEDENT IDENTIFICATION

- A priority of any autopsy is **confirmation of the identity of the decedent**
- Identification can occur in many methods:
  - **Presumptive identification:**
    - Not as reliable as scientific evidence
    - Often based on age, sex, biometric features
    - Articles of clothing/belongings
    - Unique tattoos or scars
    - Piercings
    - Family identification by viewing decedent
    - Comparison using known photographs of individual and the decedent
  - **Scientific Identification:**
    - DNA identification using blood, hair, dental pulp (in skeletal remains), or others
    - Fingerprinting
    - Dental records/comparison
      - Requires antemortem dental exam
    - Radiologic comparison
      - Requires antemortem imaging
    - Medical devices/implants
      - Often has a serial number that can be matched in antemortem records

EXTERNAL EXAMINATION FINDINGS

- Upon arrival at the autopsy suite, the body will be **photographed** as necessary for evidence
- **Utilization of a ruler and case identifier** information should be included in the photograph of each picture taken
- Distractions within photographs should be reduced or eliminated using a solid background
- For identification purposes:
  - Picture of **full face** with rule and case label/identifier should be taken
  - The overall photograph shows the **decedent clad and unclad**
  - Clean photo of the body **after being washed**
  - Photos of **belongings on and off** the decedent
  - Photographs of **key findings**:
    - Sharp force wounds
    - Gunshot wounds (entrance and exit)
    - Contusions
    - Other wounds
- **Radiographic imaging** (X-Ray or CT) should be performed in some instances:
  - To identify if the projectile is within the body
  - The extent of injuries (blunt force or penetrating)
  - Dental findings
  - Evaluation of barotrauma
  - Evaluation of air embolism
  - Estimation of age in children evaluating joint spaces or cranial suture line
  - Predicting the sex of a skeleton or decomposed body
  - Aviation deaths (especially in mass casualty)
- **Medical intervention** items
  - All medical interventions should be **left in place** for evaluation at the autopsy
  - Common items include:
    - Intravenous lines
    - Endotracheal tubes
    - Nasopharyngeal airways
    - Nasogastric and orogastric tubes
    - Surgical drains or chest tubes
    - Sutures or staples of a surgical site
    - Needle puncture marks
    - Pacemakers or defibrillators
    - External defibrillator pads
    - EKG pads
    - Urinary catheters
    - Cervical collars

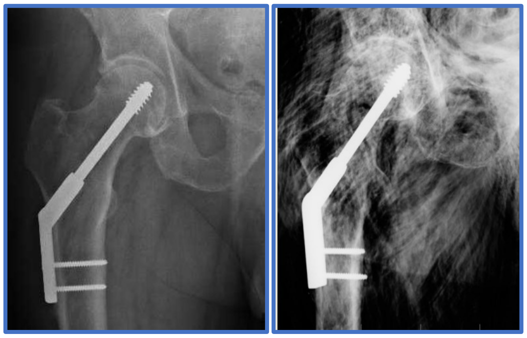


Figure: Antemortem x-ray (left) of orthopedic hardware in the left hip compared to postmortem x-ray (right) for identification. Photos used with permission from Summit County ME's Office

POSTMORTEM CHANGES

- Postmortem changes can be seen in a matter of hours after death
- Changes **can be altered or manipulated** by conditions present at the scene
  - Some findings can be accelerated, decelerated, or altered due to temperature, animal, or insect activity

- Rigor mortis **Stiffening** of the muscles due to **depletion of ATP** that muscles require to relax
    - Muscle is not shortened in Rigor mortis, unlike physiologic contraction by volition
    - Detectable at approximately **2-4 hours postmortem** and continues to develop over the first 12 hours
    - **Will remain in place for 12 hours**
    - Will begin to "break" over the following 12 hours
    - Factors that **accelerate**: Obesity, temperature, infection, and other conditions for which ATP is depleted (convulsions, electrocution, etc.)
    - Factors that **slow down development**: cold temperatures; low muscular volume (elderly, children), or carbon monoxide poisoning
- Cutis Anserina
    - Development of "**goose bumps**" due to the contraction of the arrector pili muscle attached to the hair shaft
    - It looks like "goose flesh" after feathers are plucked off
- Livor Mortis
    - **Reddish-purple discoloration** of the body due to positional hypostasis
    - Occurs due to **gravity acting on blood** within the dilated blood vessels
    - Often occurs **within the first 30 to 60 minutes of death**
    - Within the **first 12 hours, livor can be blanched**; after that, it is **fixed** due to extravasation of blood into the soft tissues and coagulation within blood vessels
    - Will occur on the **back** if decedent lying **supine**
    - If **prone** at death, lividity will occur on the **face and anterior body**
    - If suspended from **hanging,** the lividity will be seen at the **lowest points** of the body
    - If there are **pressure points**, lividity will not develop at those points due to vascular compression
        - Most commonly seen over the scapula and buttocks if lying supine
    - Factors that **accelerate** lividity:
        - Heart failure, fever and sepsis, increased temperature
    - Factors that affect the development of lividity
        - Exsanguination and anemia
    - **Abnormal lividity color**
        - Cherry Red → Carbon monoxide or cyanide poisoning
        - Brown Red → Methemoglobinemia
        - Green → Hydrogen sulfide poisoning

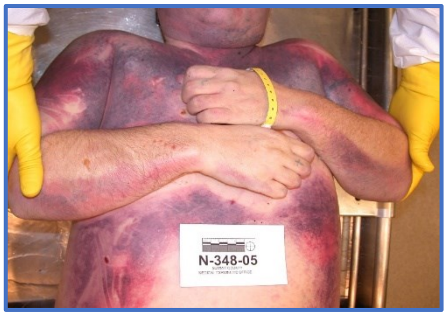


Figure: Lividity on the anterior body and lack of lividity on pressure points (arms).

- Tardieu spots
    - Are **petechia/pin-point hemorrhages**
    - Occurs due to rupture of capillaries
    - It appears over the first 24 hours
        - It can be seen **as early as 2 hours** in areas with severe congestion

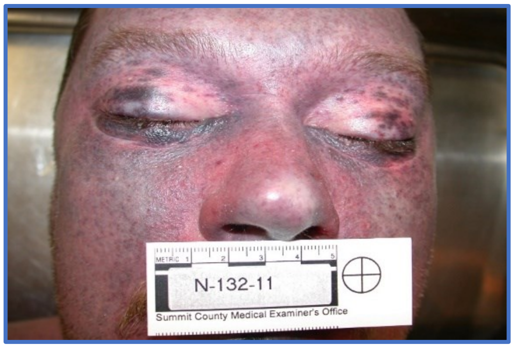


Figure: Tardieu Spots. Photo used with permission from Summit County Medical Examiner's Office

- Tache Noire
    - Postmortem drying of the sclera of the eyes that cause a black-brown or red-orange discoloration band. This is **NOT** related to trauma

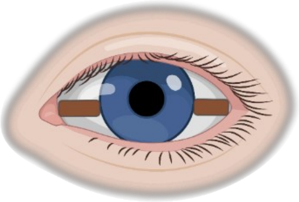


Figure: Tache noire. Created by Dr. Terrance Lynn using BioRender

- Mummification
    - **Postmortem drying** is seen in very low humidity environments
    - Bacterial growth is inhibited, and skin will dry out and **become leathery**, and change to a brown to black color
    - Can occur in **just a few weeks, especially in a desert**
- Algor Mortis
    - **Postmortem cooling** of the body
    - Highly variable and dependent on the environment that the decedent is in
    - Theoretically:
        - First 12 hours → body cooling rate is 1.5-2°F
        - For the next 12-18 hours → 1°F
    - Skin cools rapidly, so it is not the ideal organ to take the temperature
    - The most common is **rectal**, second most common is **liver**

- Autolysis & Putrefaction
  - Autolysis is the **enzymatic degradation of cells**
  - **Skin slippage** due to separation of the epidermis from the dermis and is most common at sites of pressure

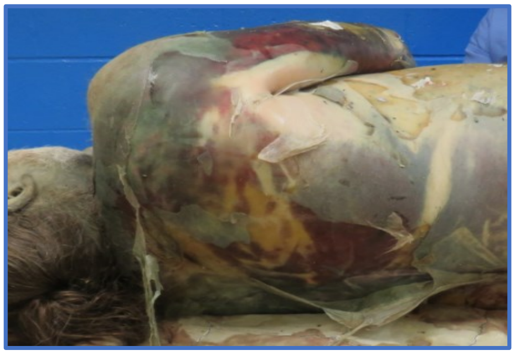


Figure: Skin slippage of the back with fixed lividity and green discoloration. Photo used with permission from Summit County Medical Examiner's Office.

  - **Putrefaction is the bacterial or fungal degradation of tissue**
    - Often due to saprophytic organisms
    - Purple to green discoloration seen in blood vessels → "**Marbling**"

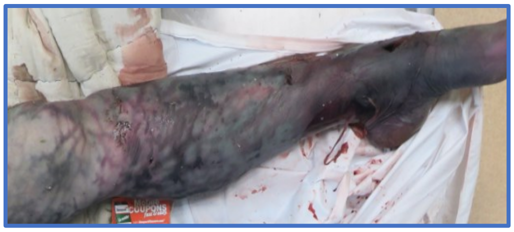


Figure: Fixed lividity with marbling of the lower left leg. Photo used with permission from Summit County Medical Examiner's Office.

- Adipocere
  - Adipose is hydrolyzed and hydrogenated and becomes "**saponified**"
  - Common causative organisms are anaerobic (i.e., **Clostridium perfringens**)
  - Generally described as a **waxy, greasy material**
    - High in glycerol and fatty acids (Palmitic, Oleic, and Stearic acids)
- Maceration
  - A systemic autolytic event seen in **stillborn**
  - Typically, skin is erythematous and has bullae

INSECT AND ANIMAL PREDATION

- **Insect activity** is variable based on the environment and temperature
  - **Maggot eggs hatch in 1-3 days** (species dependent) and give rise to the **larvae,** which feed on the rotting tissues and hasten bodily decomposition
  - Collection of the larvae or eggs should be in **70% isopropanol** for entomologic review
- **Animal Predation** is also dependent on the environment and location
  - Can be wild or domesticated animals
  - Domesticated animals (pets) often will feed on their face shortly after death
  - The wounds left by animals have scalloped edges and may show abrasions
  - Aquatic life will target exposed tissues

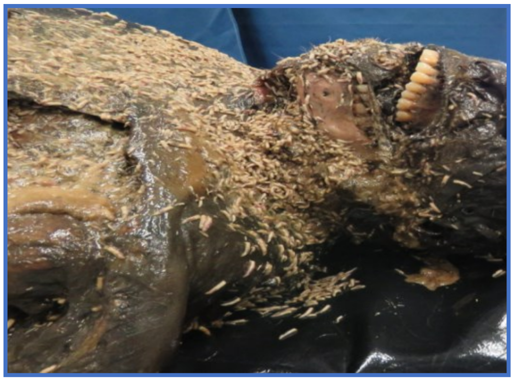


Figure: Postmortem maggot activity with numerous larval forms. Photo used with permission from Summit County Medical Examiner's Office.

POSTMORTEM CHEMISTRY

- **Changes in electrolytes** are dependent on many variables
  - Postmortem interval
  - Diseases or injuries to tissues
  - Environment
  - Putrefaction
- Many enzymes **rapidly degrade** postmortem **except** for the following:
  - Cholinesterase → can measure if suspected of intoxication/poisoning by pesticides
  - Hemoglobin
  - Serum protein→ can perform electrophoresis
- **Hormones** measurement in the postmortem are largely useless except for:
  - Thyroid-stimulating hormone
  - Cortisol
- **Vitreous humor testing**
  - Useful for testing due to the low rate of putrefaction
  - Best uses for this specimen
    - Dehydration
    - Suspicion of **Uremia**
    - Suspicion for **Diabetic Ketoacidosis**
  - Vitreous humor electrolytes:
    - **Sodium → decreases** after death

    - **Potassium → increases** after death
        - If > 15 mEq/L, this is consistent with decomposition
    - **Chloride → decreases** after death
    - **Creatinine & Urea nitrogen → generally stable** in postmortem
    - **Glucose**
        - Low or no glucose does **NOT** indicate hypoglycemia
        - Elevated level **>200 mg/dL is → hyperglycemia**
    - If ketones or acetones are present → abnormal

TOXICOLOGIC DEATHS

- The **most common** drug overdoses in the United States are due to **Opiate/Opioids**
- Upon investigation of the scene, it is essential to recognize drugs and drug paraphernalia
    - Document and photograph everything
    - Do **NOT** touch anything without gloves
        - Some drugs absorb readily through the skin and can cause effects such as overdose or death in the investigators

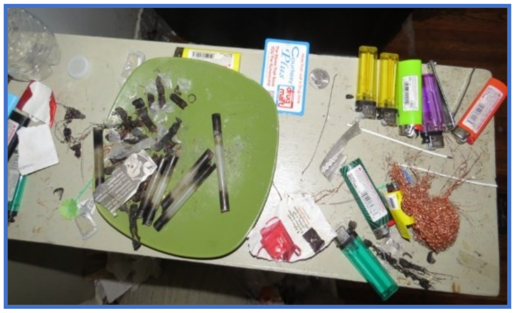


Figure: Multiple lighters, glass pipes, and other items associated with illicit drug use were found at the scene. Photo used with permission from Summit County Medical Examiner's Office.

- Examination of the body can show helpful information about drug use
    - **Puncture marks → injection sites**
    - **Track marks → old injection scars**

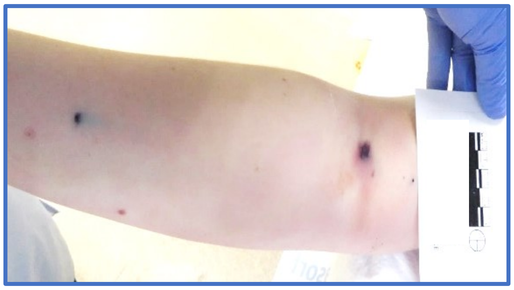


Figure: Multiple puncture sites in the antecubital fossae and along the forearm used for intravenous drug use. Photo courtesy of Kristy Waite, DO.

- Methodology for Toxicologic testing is variable and is dependent on the site
    - Emergency departments most commonly use a **urine screening test → Chromatography**
    - Clinical laboratory screening tests are often **immunoassays**
        - Has both false positives and false negatives
        - Only identify a class of drug

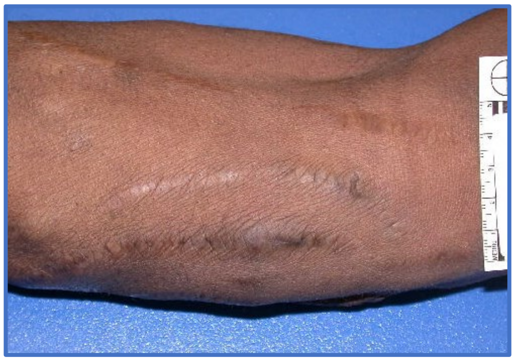


Figure: The antecubital fossae have multiple track marks (raised, linear, vascular scars). Photo used with permission from Summit County Medical Examiner's Office.

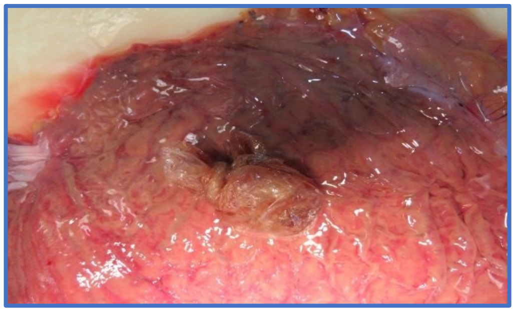


Figure: Tied and ruptured plastic bag found in the stomach of someone's body stuffing to conceal evidence. Photo courtesy of Kristy Waite, DO.

    - Forensic Analysis of Drugs
        - Quantitative method
        - Identifies specific drug
        - Usually performed using gas or liquid chromatography and mass spectrometry
- Methamphetamine/Amphetamine
    - Patients will have characteristic **dental decay** ("Meth mouth")
    - Chronic use results in increased cardiac output, hypertension
    - The cause of death is usually from **myocardial infarction**
    - May detect methamphetamine and amphetamine in confirmatory studies
- Cocaine

  - Use results increased cardiac output, hypertension, hemorrhagic stroke, delirium, and excitability
  - Classically associated with **coronary artery dissection or plaque ruptures, aortic dissection/ruptures**
  - Urine metabolite →**Benzoylecgonine**
  - Cocaine and alcohol → **Cocaethylene**
    - Highly cardiotoxic
- Heroin
  - It exists in both a white or black powder form or a black tar-like substance →"**Black tar heroin**"
  - Clinical findings can include respiratory depression, pupillary constriction, rhinorrhea, flushed skin, constipation, nausea, euphoria
  - Autopsy findings can include **froth exuding** from the mouth, urinary retention, or cerebral edema
  - **6-Monoacetylmorphine** is a specific metabolite of Heroin
    - Gray top tubes are best at preserving 6-MAM
  - Heroin has a half-life of approximately 2-6 minutes, **rarely identified in the body**
  - 6-monoacetylmorphine (6-MAM) half-life ranges from 5-40 minutes

Benzodiazepines
  - Clinically used as an anxiolytic/sedative
  - Each drug has its own type of metabolism and half-life
  - If used with ethanol, it can be lethal due to enhanced sedation
  - At autopsy, may see **pulmonary edema and foaming from the mouth or nose**
- Cannabinoids and synthetic cannabinoids
  - Includes Marijuana, THC, K2, Spice, etc
  - Most often seen in conjunction with other drugs or isolated
  - Synthetic agents are harder to test for since labs don't always validate each specific agent
- Other Opiates
  - Exist in various forms and routes of administration
  - Variable half-lives dependent on route of administration and first-pass metabolism
  - Clinical findings preceding death could include
    - Pupillary constriction, constipation, urinary retention, euphoria, sedation, bradycardia, depressed respiratory drive, hypotension, rigidity, coma

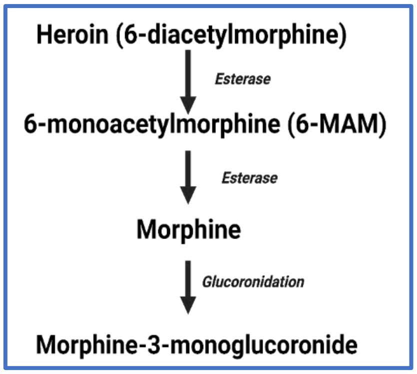

Heroin (6-diacetylmorphine)
Esterase
6-monoacetylmorphine (6-MAM)
Esterase
Morphine
Glucoronidation
Morphine-3-monoglucoronide

Figure: Heroin Metabolism. Created by Dr. Terrance Lynn using BioRender.com

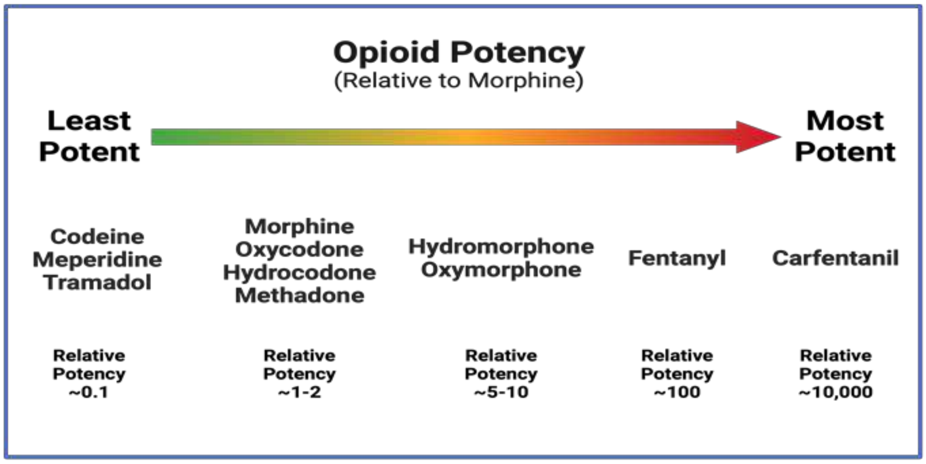
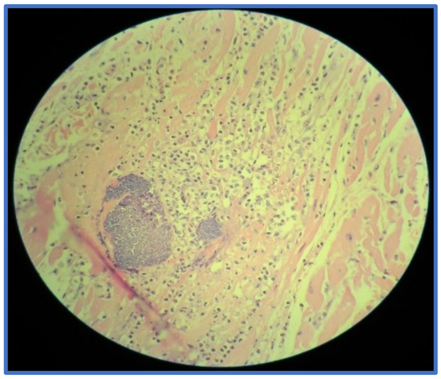


Figure: Opioid potency relative to Morphine. Created by Dr. Terrance Lynn using BioRender.com.

- Methanol
  - Most commonly seen in **illicit moonshine**
  - Metabolized into formic acid and formaldehyde
  - Retinal toxicity occurs due to the formic acid and causes blindness
- Ethylene glycol
  - A common additive in **windshield washer fluid** or other car fluids
  - Crystalizes in kidney tubules, composed of Calcium Oxalate
  - Medical treatment is the administration of **Ethanol** → don't confuse it for alcohol ingestion

Figure: Microscopic examination showing acute myocarditis, bacterial colonies, and acute inflammation. Photo courtesy of Kristy Waite, DO.



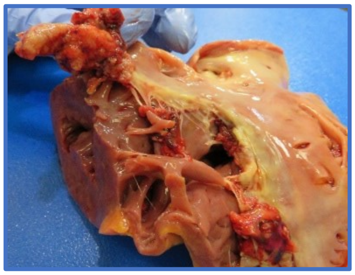


Figure: Tricuspid valve with large, diffuse vegetations from IV drug abuse. Photo courtesy of Kristy Waite, DO.

BLUNT FORCE TRAUMA AND INJURIES

- Blunt force trauma can be caused by forces that tear, shear, or crush the decedent
  - Wounds are likely to be **patterned** and reflect the causative weapon or item of injury
  - Injuries are likely due to accidents such as motor vehicle collisions, biking accidents, falls, jumping, or be from intentional assault
- **Forms of injuries include:**
  - Contusions (Bruises)
    - Seen in soft tissue, deep structures, or skin
    - May have a **negative image** of the weapon/object
  - Abrasions: Removal of superficial epidermis/skin structures and are often due to **frictional forces**
    - Types of abrasions include scratches and grazes, or brush burns
  - Laceration is a tearing of the skin
    - Wound edges are often irregular, and **tissue bridging** is seen
    - Can occur to the aorta in a motor vehicle collision due to rapid deceleration and shear force at the point of ligamentum arteriosum
  - An avulsion is the near-complete or complete **separation** of tissue from the laceration
  - A fracture is a **break of the bone** which may or may not be protruding from the skin

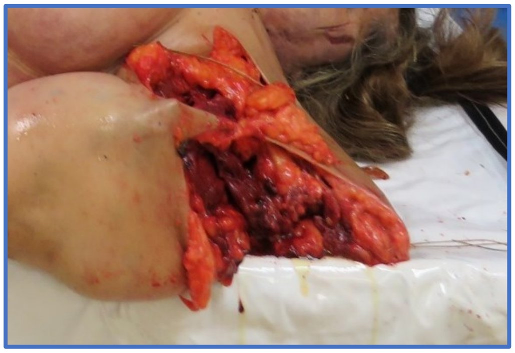


Figure: Avulsion of the soft tissue of the left upper extremity. Photo courtesy of Kristy Waite, DO.

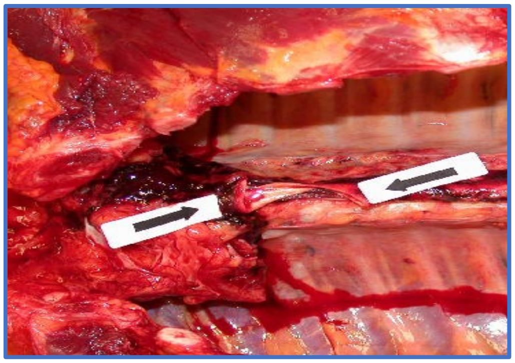


Figure: Aortic laceration from a motor vehicle collision.

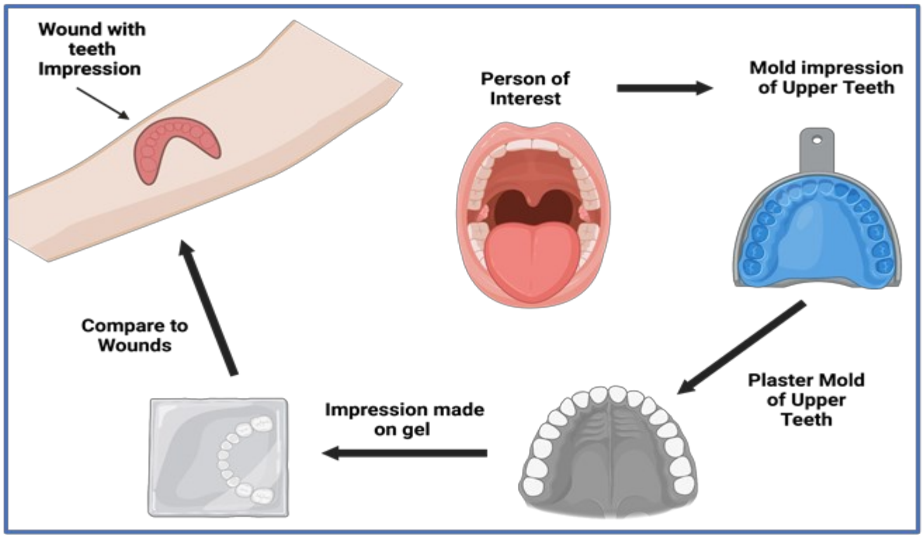

Wound with teeth Impression
Person of Interest
Mold impression of Upper Teeth
Plaster Mold of Upper Teeth
Impression made on gel
Compare to Wounds

Figure: Bite mark on decedent and method used to compare bite marks. Created by Dr. Terrance Lynn using BioRender.com.

- Bite is from either animal or human and is seen in a semicircular pattern
  - **Can collect DNA** from the wound as well as odontology studies
  - Do NOT disturb until evidence is gathered
- Contusions may also be present surrounding laceration
    - Brown or fading → weeks to a maximum of 2 months
  - Approximate **aging based on microscopic findings**
    - Margination of Leukocytes → minutes to 4 hours

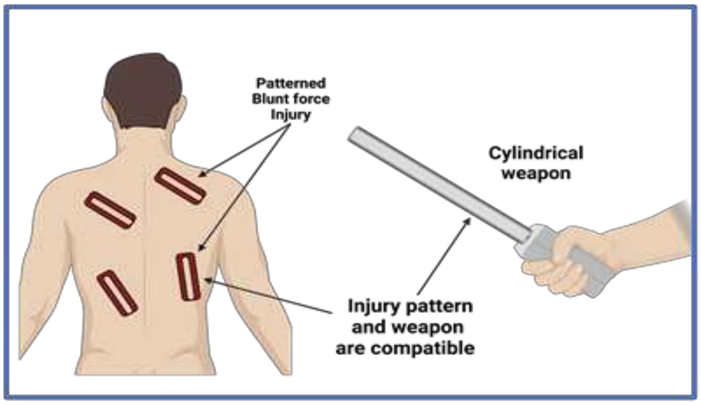

Patterned Blunt force Injury
Cylindrical weapon
Injury pattern and weapon are compatible

Figure: Comparison of a “Tram-track” patterned injury with a cylindrical weapon. The weapon and patterned injury are compatible. Created by Dr. Terrance Lynn using BioRender.com.

BLUNT FORCE TRAUMA TO CENTRAL NERVOUS SYSTEM

- Blunt force trauma to CNS can be devastating and cause fractures and hemorrhages
- Injuries can be localized or diffuse
- Can occur from various types of trauma
  - Motor vehicle collisions
  - Gunshot wounds to head
  - Traumatic falls
  - Striking the head
- Epidural hemorrhage/hematoma
  - Occurs between the cranial bones and the dura
  - Caused by **shearing/tearing of the arteries** from fracture of skull bones
    - Often the **Middle Meningeal artery** in cases of temporal bone fracture
    - It can happen in children **without** having a skull fracture
  - Causes increased intracranial pressure and ultimately cerebral ischemia and cerebellar herniation
- Subdural hemorrhage/hematoma
  - Occurs between the dural layers
    - Dura has a cellular fibroblast layer and a collagenous layer

  - May contain foreign material from the weapon or the environment
  - Approximate **aging based on gross color**
    - Light blue/red → hours
    - Purple → days
    - Yellow green → 1 week
    - Mononuclear cells → 12 hours
    - Neovascularization → ~24 hours
    - Iron staining→ 24 hours to 36 hours
    - Collagen formation → 5 days
    - Elastic fibers → weeks

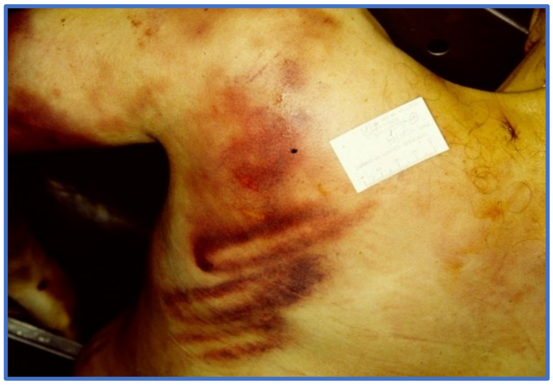


Figure: Blunt force (“Tram-track”) patterned injury from a cylindrical object. Photo used with permission from Summit County Medical Examiner’s Office.

  - Caused by traumatic injury in which the **bridging veins are sheared**
    - Can be minor trauma in the setting of **elderly or children**
  - Gross aging of hematomas depends on its size but generally:
    - Clot formation → 4 days
    - Clot adherence to dura → >4 days

    - Brown discoloration and degeneration occur at 1 to 2 weeks
    - The formation of the outer membrane occurs between 2 and 4 weeks
    - Complete formation of outer membrane → ~8 weeks
    - Yellow-Brown color and motor-oil liquefication → months to years
  - **Microscopic aging of subdural hematomas**
    - Capillary dilation and neutrophils occur in the first 24 hours
    - Fibroblastic proliferation at 2-3 days
    - Thin fibrin layer → around day 5
    - Hemosiderin and red cell breakdown, macrophages, capillary formation → Day 10

        - The true inner membrane, connective tissue maturation → 4 weeks

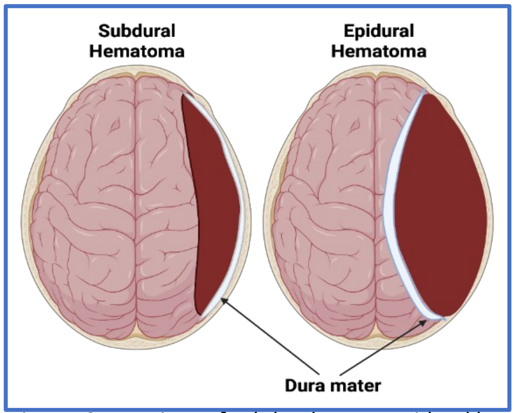

Subdural Hematoma
Epidural Hematoma
Dura mater

Figure: Comparison of subdural versus epidural hematomas. Created by Dr. Terrance Lynn using BioRender.com.

- Subarachnoid hemorrhage/hematoma
    - Usually from a cerebral contusion or trauma
    - Can be a result of a **vascular malformation or congenital disorder** (i.e., **Ruptured Berry Aneurysm** in the setting of polycystic kidney disease)
    - The amount of blood is variable in space

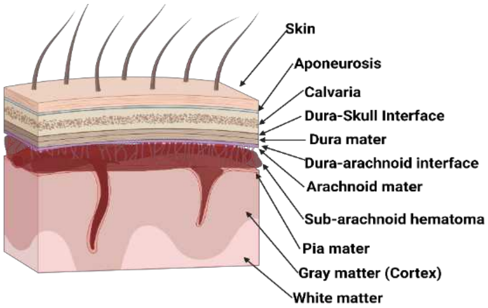

Skin
Aponeurosis
Calvaria
Dura-Skull Interface
Dura mater
Dura-arachnoid interface
Arachnoid mater
Sub-arachnoid hematoma
Pia mater
Gray matter (Cortex)
White matter

Figure: Diagram showing a subarachnoid hemorrhage. Created by Dr. Terrance Lynn using BioRender.com.

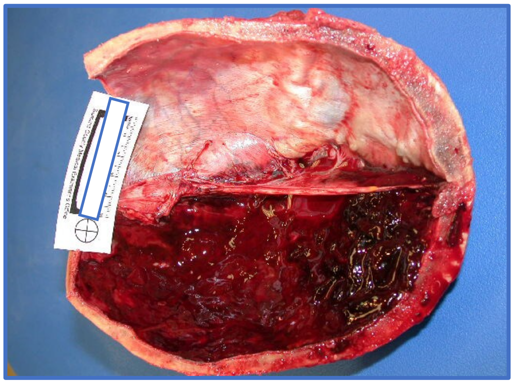


Figure: Acute to subacute subdural hematoma. Photo used with permission from Summit County ME's Office.

- Intraparenchymal hemorrhage
    - A variety of medical diseases can cause it
        - Embolic even then, bleeding
        - **Hypertension and rupture of small vessels** within basal ganglia, deep nuclei, thalamus, pons, cerebellum, or ventricles
        - Cerebral **amyloid angiopathy**
        - Trauma

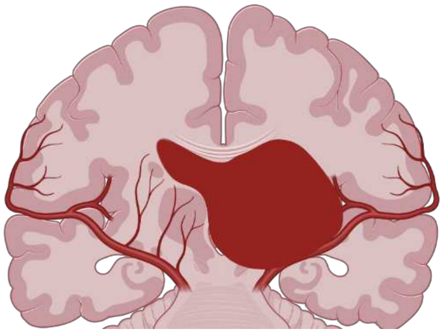


Figure: Diagram of an intraparenchymal hemorrhage. Created by Dr. Terrance Lynn using BioRender.com.

- Cerebral contusions
    - Occur from any **physical force** that is exerted upon the skull/brain
    - Can enlarge over time from continued bleeding or worsening coagulopathy
    - Cerebral cortical contusions usually demonstrate:
        - **Streak-like or punctate hemorrhages** and necrosis are **restricted to a gyrus or sulci crests**
    - May have a "coup" and "contrecoup" injury pattern
        - **Coup** → contusion occurs **immediately adjacent** to the site of impact
        - **Contrecoup** → contusion **opposite** to initial injury site

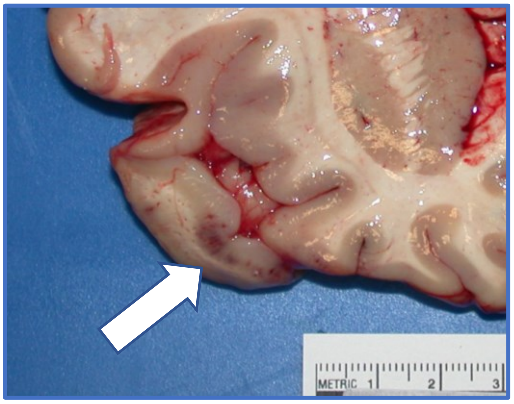


Figure: Contusion of the inferior temporal lobe. Photo used with permission from Summit County ME's Office.

SHARP FORCE INJURIES

- Sharp force wounds are **penetrating injuries** caused by objects with an edge that can pierce or cut tissue
- Typically wounds from sharp forces have the following features

  - Lack of abrasion and tissue bridging
  - Are often without contusion
    - Except where part of the object hits the skin
  - Have **clean-cut edges**
- Sharp force wounds can be classified into the following
  - Incised wounds
  - Stab wounds
  - Patterned wounds
  - Dicing wounds
  - Chop wounds
  - Hesitation and cutting wounds
  - Defensive wounds
- Incised wounds
  - Caused by a sharp or pointed object and leaves a **linear wound**
  - The wound is **longer than it is deep**
  - The object may or may not be serrated
- Stab Wounds
  - Caused by a sharp or pointed object and leaves a linear wound
  - The wound is **deeper rather than long**
  - The object may have a **single or double sharp edge**, which will change wound borders
  - The object may or may not be serrated
- Patterned wounds
  - Caused by a sharp object which has repetitive patterns on the object
  - Objects can include Phillips screwdrivers, utensils/cutlery, bow and arrows, scissors, etc.
- Dicing wounds
  - Caused by fragments of glass that knick the skin surface
  - Often seen in the context of a motor vehicle collision where windshield glass breaks

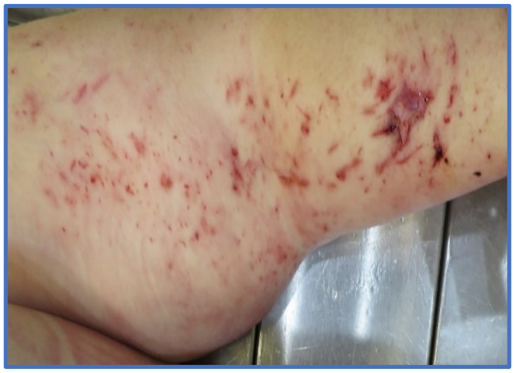


Figure: Dicing injury of the left arm. Photo courtesy of Kristy Waite, DO.

- Chop wounds
  - Caused by an object that has **both sharp and blunt edges** and **is associated with a bone fracture**
  - May or may not have blunt force findings such as contusions, abrasions, or lacerations
  - It can be seen in items such as axes and boat propellors

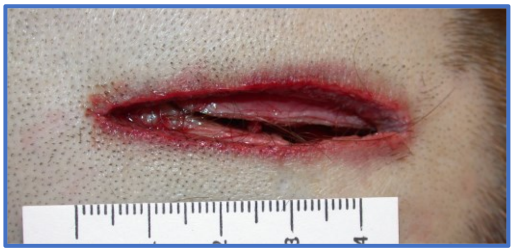


Figure: Chop wound of the head. Photo used with permission from Summit County ME's Office.

- Hesitation and cutting wounds
  - Caused by self-harm activities such as cutting
  - Often the **initial wound is shallow and has an irregular pattern** → Believed to be due to the hesitation from self-inflicted pain
  - Frequently seen in suicides, especially among teen females
  - Often occurring on the **neck or wrists**
  - Scars identify previous sites of injuries
  - Often this is not a fatal wound but may be a **precursor to a fatal wound**

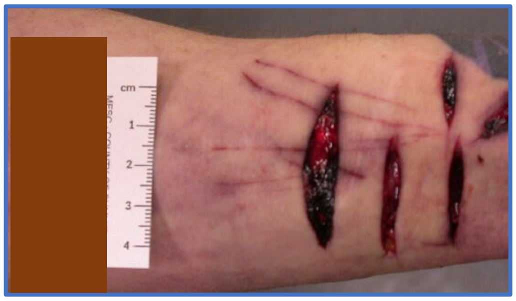


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Figure: Hesitation wounds on the wrist. Photo used with permission from Summit County ME Office.

- Defensive wounds
  - Seen in actions of self-protection from harm
  - Most commonly seen in homicides as victims are trying to protect themselves. May be seen on **palmar hands, anterior arms, or forearms**

GUNSHOT WOUNDS

- Gunshot wounds can be non-fatal or fatal wounds
- Not every entrance wound will have a corresponding exit wound → still within the decedent's body
- There are many different types of guns
  - **Handguns**
    - Revolvers, Pistols
  - **Long guns**
    - Musket, Carbine, Shotgun, Rifle
- Wounds left by a projectile will leave permanent and temporary cavities

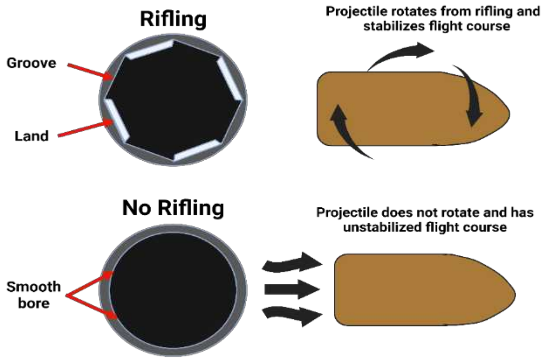
Rifling
Groove
Land
Projectile rotates from rifling and stabilizes flight course
No Rifling
Smooth bore
Projectile does not rotate and has unstabilized flight course

Figure: Explanation of rifling and its purpose. Created by Dr. Terrance Lynn using BioRender.com

- Rifling in long guns is beneficial because of the ability of the projectile to **rotate around an axis**, and thus it stabilizes projectile flight
- Without rifling in a long gun, the projectile has an unstable flight course
- **Various materials can also be discharged** from the gun along with the projectile
  - Bullet fragments, Lubricant, Soot, Flames and flashes
- **Entrance wounds** characteristics
  - Have a punched-out appearance
  - May have stippling
  - May have beveling (seen in skulls)
  - The caliber of the gun cannot be identified based on the entrance wound
- The entrance wounds will look different based on the proximity of the shooter and the victim
- **Contact/close range**
  - Can leave a muzzle imprint
  - Soot is present on the skin surrounding the entrance and, in the wound
  - May have radiating lacerations around the wound

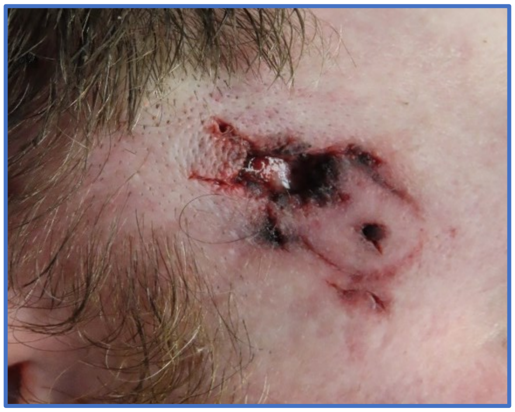

Figure: Hard contact gunshot entrance wound with muzzle imprint, marginal abrasion, and soot. Photo used with permission from Summit County ME's Office

- **Intermediate range**
  - The weapon is near the victim, leaving **punctate abrasions** surrounding the entrance wound, from pieces of gunpowder striking the skin → stippling
  - Seen in ranges of inches to about 4 feet
    - Dependent on the firearm and ammo used
  - The further away the shooter is, the larger the stippling pattern
    - At a certain point, too far away for stippling
  - Pseudo stippling → abrasions from fragmented bullets or another object (s) that were between weapon and target
- **Indeterminate/ distant range**
  - A firearm is at a distance where **no soot or gunpowder** reaches the skin, so only the bullet makes a wound
  - Wounds can look like a distant range if something else is between the weapon and the wound, like clothing, hair, curtains, etc.

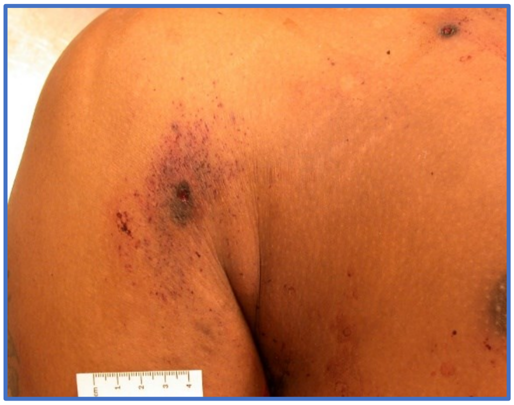

Figure: Intermediate-range gunshot wound with stippling (right shoulder) and distant/indeterminate range gunshot wound (right upper chest) with no soot or stippling. Photo used with permission from Summit County ME's Office

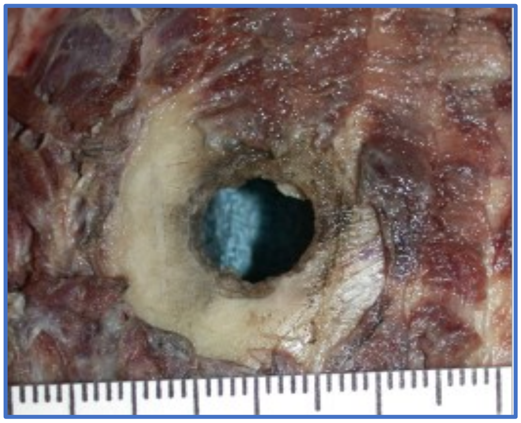

Figure: Entrance gunshot wound of the skull. This is the outer table of the skull with muscle visible and sharp edges of the damage with soot present. Photo used with permission from Summit County ME's Office.

- **Graze wounds**
    - From tangential striking of skin from the projectile which makes a superficial wound
    - Lacerations point towards the direction of projectile travel, skin tags point to the origin of projectile

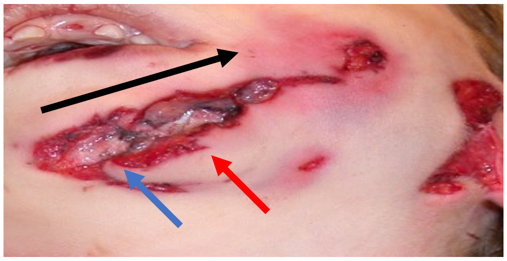

Figure: Graze wound on the left chin. (Blue arrow → skin tag; red arrow → laceration; black → direction of the projectiles). Photo used with permission from Summit County Medical Examiner's Office.

- Exit wounds
    - **Often irregular lacerations and may be stellate**
    - **No soot** will be present, no abrasion (unless shored)
    - May have multiple exit wounds if there is the fracturing of the projectile

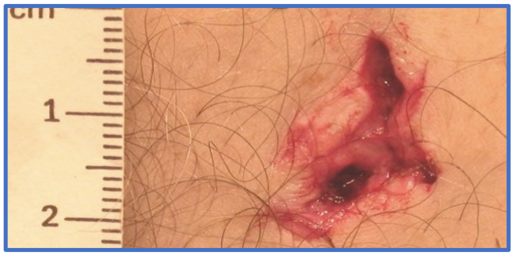

Figure: Shored exit showing surrounding abrasion and irregular shape. Photo used with permission from Summit County Medical Examiner's Office.

- Another injury from ballistic weapons can be the **shell or gun wadding**, this often leaves distinct marks and can be photographed and compared to ballistics later in the investigation

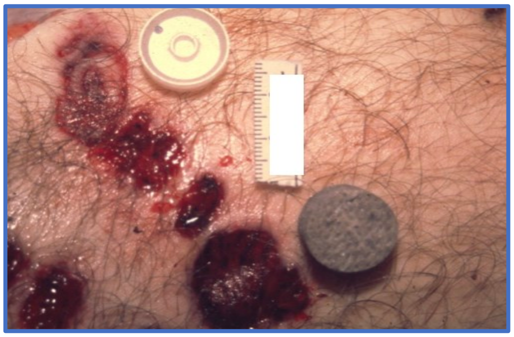

Figure: Shotgun shell wadding and associated injuries. Photo used with permission from Summit County ME's Office.

- Exit wounds can be re-approximated at the time of autopsy

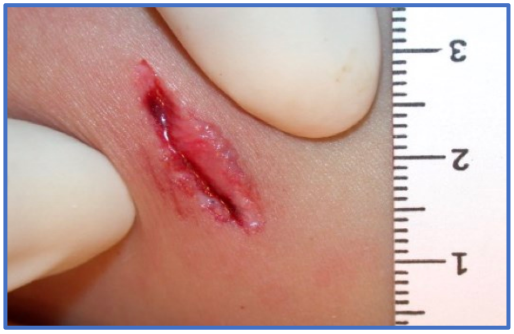

Figure: Reapproximating an exit wound. Photo used with permission from Summit County ME's Office.

ASPHYXIAL DEATHS

- Asphyxiation can be caused by the following
    - Environmental factors: Gases such as Cyanide, Carbon monoxide, Hydrogen sulfide, enclosed spaces with low oxygen, mechanical asphyxiation, smotherin, drowning, hanging, choking, crucifixion, ligature strangulation, manual strangulation
- Not all forms of asphyxiation will leave marks on the decedent's body
    - Some findings are nonspecific, like cyanosis, petechiae, abrasions

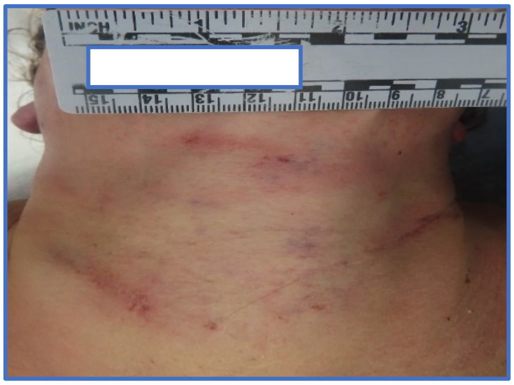

Figure: Bilateral curvilinear abrasions on the neck from strangulation. Photo courtesy of Kristy Waite, DO.

- Scene information and circumstances are critical in the determination of the manner as well as the cause of asphyxiation
- Confined/Enclosed spaces
    - Cause asphyxiation due to reduced O_2 environment with **lack of O_2 exchange**
- Mechanical Asphyxiation
    - Causes asphyxiation by **restriction of chest movement** that does not allow for adequate inhalation
    - Either traumatic or positional

- Smothering
  - Causes asphyxiation by the **inability of O2 to reach the lungs,** usually from pillows or blankets
- Drowning
  - Causes asphyxiation by **filling the lungs with water and preventing the exchange of gasses**
- Hanging
  - Causes asphyxiation by c**ompression of neck** by some or all the decedent's weight on a rope or other item
    - Judicial hanging → **fractures neck**
  - It does not require suspension to occur
  - Hyoid bone does not need to be fractured
    - On test → always fractured
  - Death occurs when the force on the head and neck exceeds **13.6 kg (~30 lbs.)** of pressure
  - **Venous** occlusion occurs at **4 lbs.** of pressure
  - **Arterial** occlusion of carotids occurs at approximately **10 lbs.** of pressure
  - **Tracheal collapse** occurs at **20 lbs.** (of pressure
  - **Occlusion of vertebral arteries** occurs at approximately **35 kg** of pressure
- Choking
  - Causes asphyxiation by **blockage of the trachea** and preventing adequate oxygen passage
  - Often seen in children or elderly
- Crucifixion
  - Causes asphyxiation by **exhaustion**
  - Stretching of arms in an outward position which prevents adequate respiration while lower extremities hang
- Ligature strangulation
  - Causes asphyxiation by an **external force** (unrelated to weight of the decedent) that is compressing the trachea
- Manual strangulation
  - Causes asphyxiation by **external force** (assailants' hands, arms, feet) that compresses the decedent's trachea

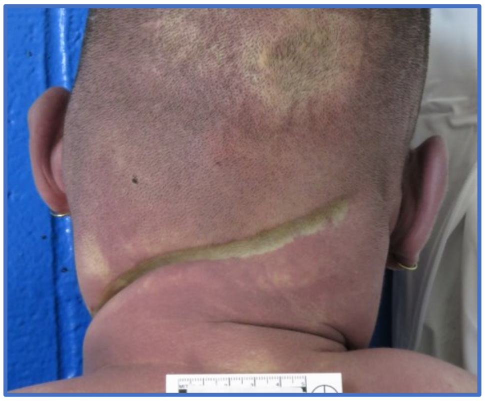

Figure: Upward angled ligature furrow with impression in the skin. Photo used with permission from Summit County Medical Examiner's Office.

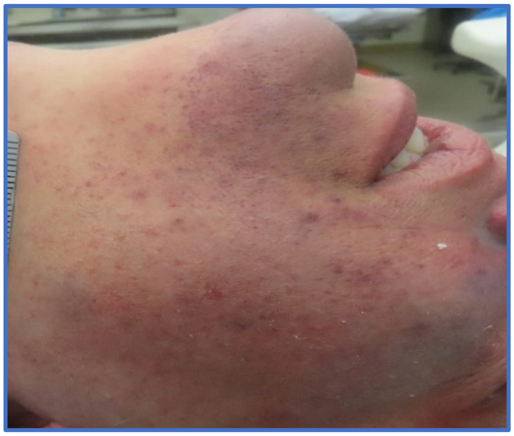

Figure: Florid petechiae across the face. Photo courtesy of Kristy Waite, DO.

- Gases in the atmosphere
  - Causes asphyxiation by **absence of O2**
  - May be from chemicals in the atmosphere or chemicals that poison cellular mechanisms of respiration
  - **Carbon monoxide**
    - 'Normal' level in smokers: 3-10%
    - >30% is toxic; less is needed if cardiorespiratory disease present
    - 'Cherry-red' lividity and tissue color (muscles, blood, etc.)
    - Necrosis of the globus pallidus can be seen
    - Causes death due to the preferential binding of CO to hemoglobin and thus prevents O2 binding
  - **Cyanide**
    - The bitter almond odor that not everyone can smell
    - Binds and blocks cytochrome A3 stopping aerobic metabolism → hemoglobin can't release oxygen
    - Bright red discoloration of tissues
  - **Hydrogen sulfide**
    - Rotten egg odor
    - From organic decomposition (sewers), industry (rubber, leather), and natural (caves, volcanoes)
    - Blocks cytochrome oxidase
    - Departs a green discoloration of the skin and tissues

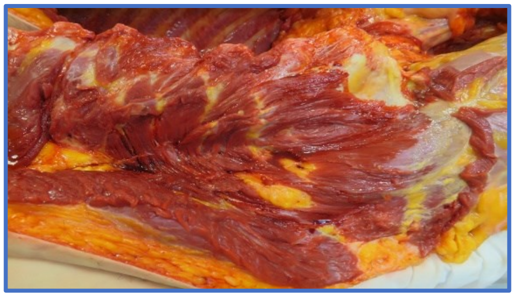

Figure: Cherry-red tissue discoloration of skeletal muscle. Photo courtesy of Kristy Waite, DO.

17. FORENSIC PATHOLOGY

ELECTROCUTION

- Not a very common mechanism of death despite the widespread use of electricity and appliances
- Can occur from **electrical lines or by lightning strikes**
- Several aspects of electrocution can cause death
    - Current
    - Secondary injury (falls from powerline)
    - Blast effects
    - Temperature
- **Current related death**
    - Cardiac arrhythmias → Ventricular fibrillation
    - Respiratory arrest → brainstem or paralysis of the diaphragm
    - Muscle tetany
- **Blast effect**
    - Seen in lightening as well as high voltage
    - Internal organ rupture and skin denudement
- **Thermal-related death**
    - High voltage (short exposure)
        - Considered 1000 V or greater
    - Low voltage (prolonged exposure)
        - Considered 1000 V or less
- Households are low voltage at 120 V
- Residential lines are 7500 V
- High-tension wires are 100,000 V or more
    - **Direct current (DC) is less dangerous than alternating current (AC)**
    - Often seen in cases with work-related fatalities on powerlines or power components
- It takes **only seconds for electricity to be fatal**
- Current flow is the most critical factor in electrocution – measured in amperage
    - The current takes the flow of least resistance through the body
- Lightening is usually high temperature and has a high current
    - Up to 20,000^{O}C in temperature
    - Up to 30 kA
- Death from lightening occurs from **cardiac arrest and electrothermal injuries**
- Scenes will usually show clothing that has been blown off of decedent from lightening
- Can frequently show **entrance and exit sites** (usually feet), with singed hair, tissue damage, and ruptured eardrums
- **Lichtenberg figures**
    - The characteristic finding in lightning strikes
    - Not commonly seen, but when present, pathognomonic for lightning
    - It is a **fern-like pattern** from intravascular hemolysis within the capillaries/veins that can disappear within 24 hours

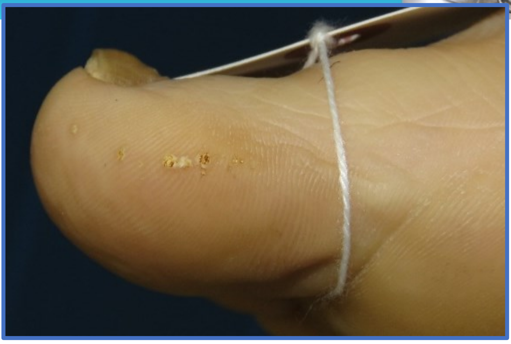

Figure: Tiny white, dot-like blister from electricity. Photo used with permission from Summit County Medical Examiner's Office.

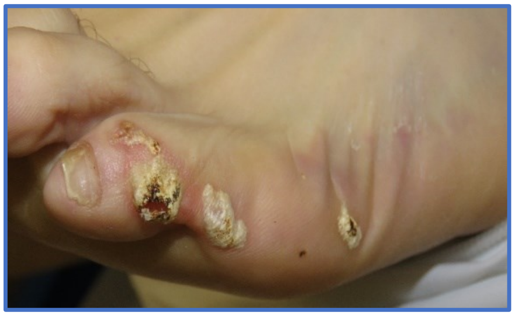

Figure: Chalky-white, blister-like lesions from electricity. Photo used with permission from Summit County ME's Office.

EXPOSURE RELATED DEATHS

- Not a common cause of death but is seen when there are **temperature extremes**
- Reliant on a circumstance such as a scene environment, weather, and location
- Different ages are susceptible based on the following
    - Body habitus
    - Underlying medical conditions
    - Drug and alcohol use
    - Length of time of exposure
- Hypothermia
    - Cooling of the body below 95^{O}F (35^{O}C)
    - Severe hypothermia (<80^{O}F) has a 10% survival rate
    - Primary hypothermia → environment
    - Secondary hypothermia → underlying medical conditions with dysregulation of temperature
    - It affects the spinothalamic tract and hypothalamic nuclei
    - The body compensates with vasoconstriction
    - **Cardiac function alteration**
        - Bradycardia
        - Prolonged QRS and inverted T-waves
        - Blood pressure declines at 93 ^{O}F
        - Increased myocardial oxygen consumption
    - **Respiratory abnormalities**
        - Respiratory acidosis
        - V/Q mismatches
            - Increased dead space

    - Decrease in tidal volume
    - Progressive decline in respiratory rate
  - **Nervous system alterations**
    - Impaired judgment, cognition, and arousal
    - Slurred speech
    - Loss of higher-cortical skills
    - Increased muscle tone
    - Shivering
  - **Renal abnormalities**
    - Renal tubule function declines
    - Relative central hypovolemia
      - Vasoconstriction at periphery
  - **Hematologic abnormalities**
    - Hypostasis and increased viscosity
    - Hypercoagulability due to reduced enzyme functions below biological function temperatures
  - **Frost Erythema**
    - Discoloration of knees, hands, and feet from agonal movement

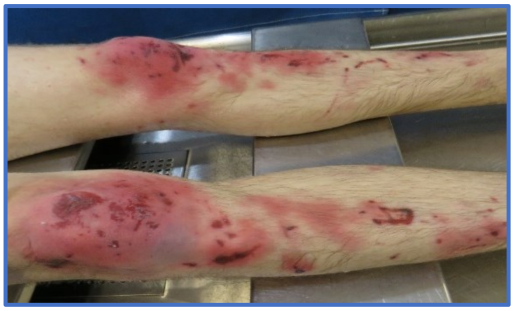

Figure: Frost erythema. Photo used with permission from Summit County Medical Examiner's Office

  - **Wischnewsky Spots**
    - Superficial punctate hemorrhages are seen in the stomach

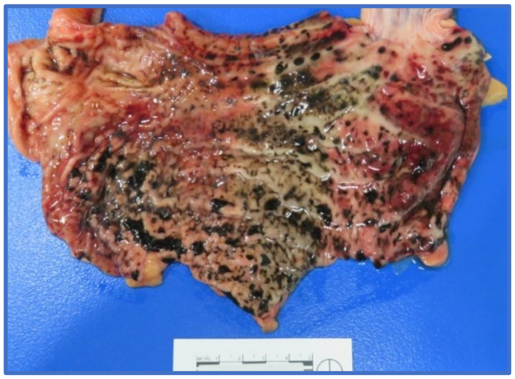

Figure: Wischnewsky Spots. Photo used with permission from Summit County Medical Examiner's Office

- Hyperthermia
  - The elevated temperature of the body above 104^{O}F
  - Can be caused by the environment, drugs, or metabolic disorders
    - Environment → inside of cars, deserts, etc.
    - Drugs → Uncoupling agents
  - Autopsy findings include:
    - Petechial hemorrhages on viscera
    - Transmural cardiac infarctions
    - Subendocardial hemorrhages
    - Cardiac myocyte degeneration
    - Liver congestion
    - Cerebral edema
    - Ventricular petechial hemorrhages

THERMAL RELATED DEATHS

- Less than 5,000 deaths/yr. from fires are seen in the US
- Thermal deaths include those
  - **Dry heat injuries → Burns**
    - Caused by fires
  - **Wet heat injuries → Scalds**
    - Caused by hot liquids or gases
- An unelevated CO level does not exclude that the individual was alive at the time of the fire
- The absence of soot in the airway does not definitively indicate that the individual was dead before the fire
- Both children and the elderly are highly susceptible to thermal-related deaths
- **Findings at autopsy**
  - First degree burns
  - Second-degree burns
  - Third-degree burns
  - Fourth-degree burns
  - Pugilistic posturing, soot in airways
  - Heat hematomas
- **First-degree burn**
  - Thermal injury is limited to the epidermis and only has erythema
- **Second-degree burn**
  - The thermal injury involves the epidermis and papillary dermis
  - Will have blisters at the site of injury
- **Third-degree burn**
  - Full-thickness integument injury
- **Fourth-degree burns**
  - The integument is largely charred
- **Fire-related death mechanisms**
  - Tracheobronchial injury from superheated gasses and soot inhalation
  - Carbon monoxide poisoning
  - Reduced O_2 environment with other gasses
    - Carbon dioxide
    - Cyanide
    - Phosgene
- **Pugilistic posturing**

  - The posturing of the body as if the decedent were "boxing"
  - Caused by flexor muscle contraction
  - Occurs regardless of dead or living at the time of the fire
  - It is seen in both upper and lower extremities

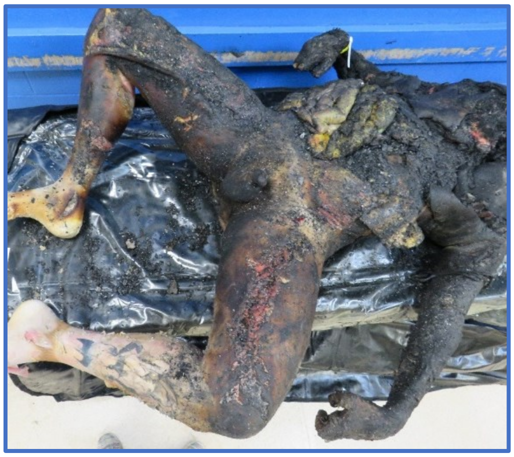

Figure: Pugilistic posturing of lower extremities. Photo used with permission from Summit County ME's Office.

- **Heat Hematoma**
  - Artifactual hematomas that occur due to overlying **charring of calvarium**
  - May accompany a postmortem fracture
  - Often **appear as "epidural" hematomas** and will have a red to chocolate brown appearance
  - Postmortem CO levels in hematoma are comparable to blood CO levels

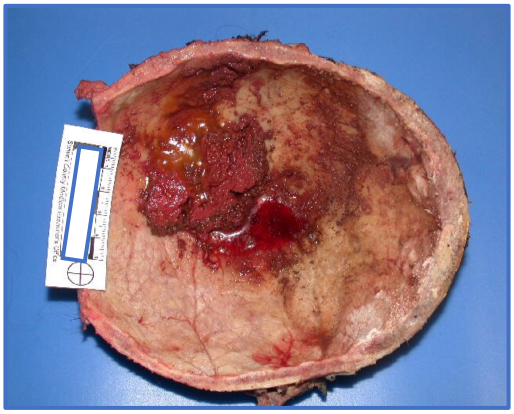

Figure: Artifactual epidural hematoma from fire. Blood red-brown and is thick and crumbly. Photo used with permission from Summit County Medical Examiner's Office.

- **Soot and Combustible debris in Trachea**
  - Occurs due to smoke inhalation
  - May have little or a large amount of soot
  - The absence of it in the trachea does not exclude that they were dead at the time of the fire

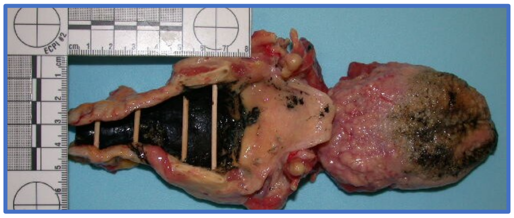

Figure: Soot and combustion material present on the tracheal mucosa and tongue. Photo used with permission from Summit County Medical Examiner's Office.

CHILD DEATHS

- It can be a result of abuse, neglect, congenital abnormalities, or unexplained
- Child death is complex due to various factors and emotions present (family and medical team)
  - Nearly 1 in 7 children are abused, and it occurs in all socioeconomic statues
  - Many homicides involve a family member who has a known history of domestic violence
  - Mothers tend to be perpetrators of infant killing through suffocation and strangulation
  - Fathers tend to be the perpetrators of the killing of older children through beating, stabbing, and shooting
- **Injury patterns** include the following
  - Sexual assault
  - Emotional abuse
  - Physical abuse
- The investigation is critical and often requires scene reconstruction, thorough interviews, and an extensive and well-documented autopsy
- Autopsies require specialized dissection of all contusions and sites of injury
  - Highly disfiguring but essential for documentation to identify mechanisms
- **Radiographic imaging** is necessary to examine for fractures and evaluation of growth plates
- **Sudden Infant Death Syndrome (SIDS)**
  - Death in an infant less than one year
  - Diagnosis of exclusion = absolutely no causes of death found after a complete autopsy, cultures, toxicology, scene visit, and review of medical records
  - Cause and manner are usually undetermined; manner can also be natural since all others have been excluded
  - Risk factors include premature birth, male sex, maternal smoking
- **Thermal injuries**
  - Usually found in potty training age – around 1-2 years old
  - Correlating physical injury patterns with story is crucial
  - Scald burns result in one-fourth the amount of time for full-thickness burns than in an adult
  - Sparing may be present in areas that are pressed against

something – ex. buttocks to the bottom of the tub

  - Glove and stocking patterns with clear-cut immersion lines can be seen on feet and hands
  - Can be patterned from different objects
    - Circular from cigarettes, car cigarette lighters, iron, etc.

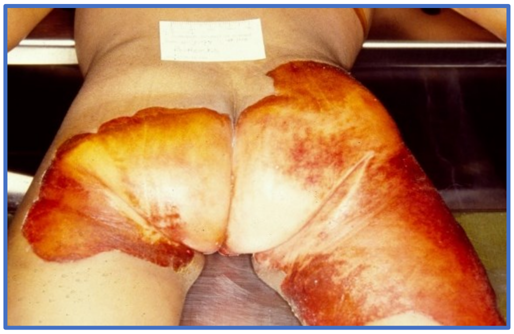

Figure: Child with an immersion burn on buttocks and right upper leg. Photo used with permission from Summit County ME's Office.

- **Child abuse**
  - The thorough examination must be complete, including unroofing the orbits, reflecting the skin from the extremities and torso, taking histological sections, cultures, specimens, radiographs, etc.
  - **Rib Fractures** that are suspicious for abuse
    - Posterior rib fractures
    - Humerus fractures
    - Femur fractures
    - Multiple and compressed skull fractures suggest abuse, especially with internal cranial trauma
    - Diaphyseal spiral fractures suggest inflicted trauma
    - Multiple fractures in different stages of healing with acute fractures are highly likely for abuse
  - Fractures that are **NOT** suspicious but are **likely accidental**
    - Single fractures, linear fractures, parietal skull fractures. Tibial fracture (aka 'Toddler's fracture') is a nondisplaced fracture → accidental
  - Other findings suggestive of abuse
    - Diffuse axonal damage
    - Subdural hemorrhage, subarachnoid hemorrhage,
    - Retinal hemorrhages
    - Optic nerve hematomas

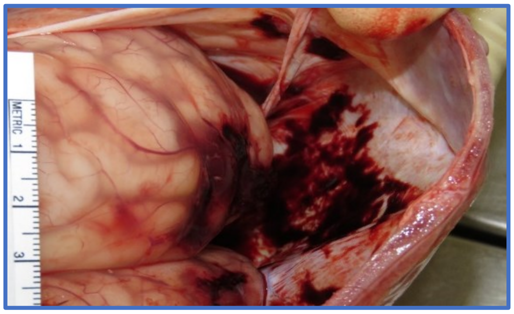

Figure: Posterior subdural hemorrhage. Photo used with permission from Summit County Medical Examiner's Office.

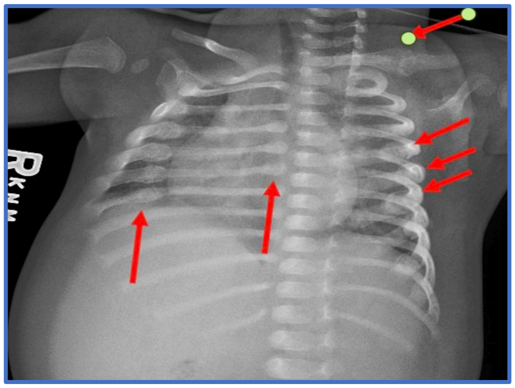

Figure: X-ray demonstrating bilateral rib fractures along the bilateral posterolateral aspects, the right posterior spine, and a left clavicle fracture. Photo used with permission from Summit County Medical Examiner's Office.

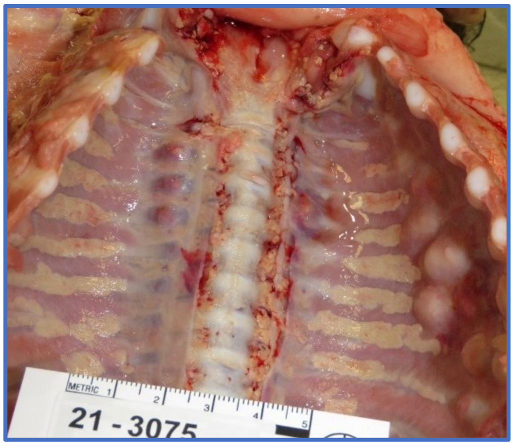

Figure: Gross photo of the same case from the above x-ray showing posterior and posterolateral bilateral rib fractures with various stages of healing. Image used with permission from Summit County Medical Examiner's Office.

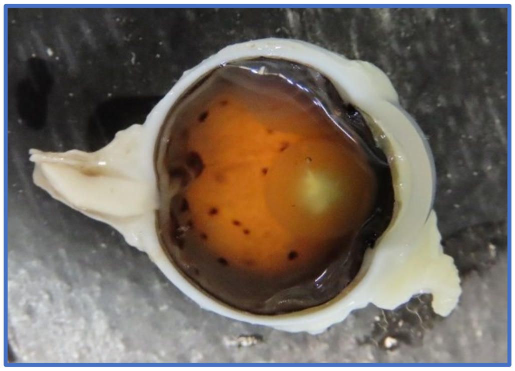

Figure: Gross examination of eye showing retinal hemorrhages. Photo used with permission from Summit County ME's Office.

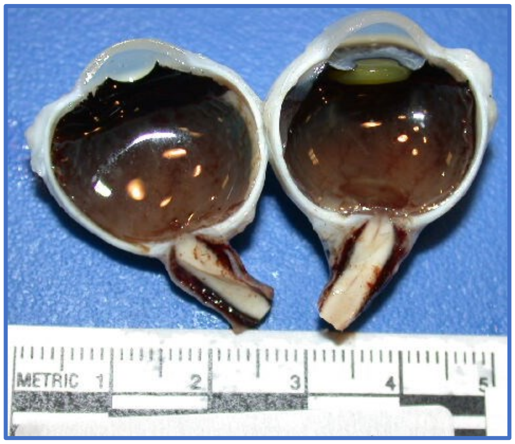

Figure: Gross examination of bilateral eyes and optic nerves showing bilateral nerve sheath hemorrhages. Photo used with permission from Summit County Medical Examiner's Office.

References:

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- Spitz, W. U. (2020). *Spitz and fisher's medicolegal investigation of death* (5th ed.). Charles C. Thomas Publisher.
- DiMaio, V. J. M. (2015). *Gunshot wounds: Practical aspects of firearms, ballistics, and forensic techniques, third edition* (3rd ed.). Productivity Press.
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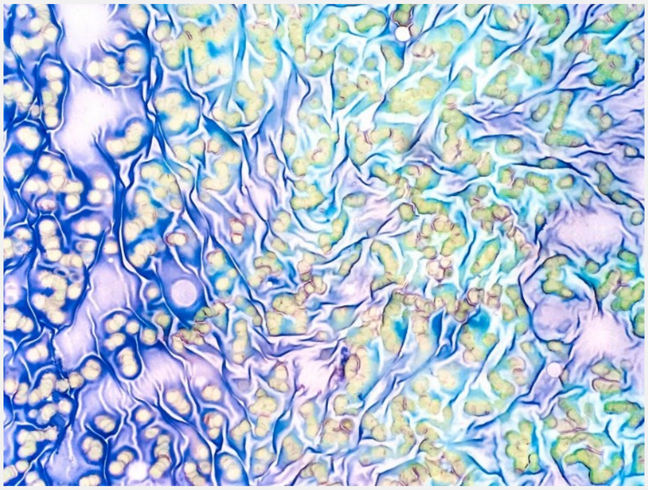

Giemsa stain in a particularly over-stained area - a beautiful Artifact. Image courtesy: Ziad El-Zaatari, MD

CHAPTER 18: MOLECULAR PATHOLOGY

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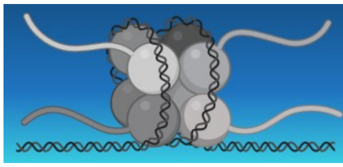
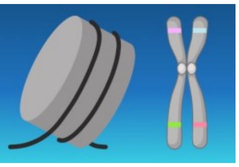


18. MOLECULAR PATHOLOGY



INTRODUCTION

- Molecular diagnostics has become increasingly important over the last decade
- Information generated from such testing provides confirmation of diagnosis, prognosis, and identifies mutations for which targeted therapy exists
- Selection of specimens for molecular testing depends on current guidelines, clinical decision making, and what each molecular pathology lab offers in their test catalog

NUCLEOTIDES AND NUCLEOSIDES

- Basic building blocks are nucleosides: Adenine (A), Guanine (G), Cytosine (C), and Thymine (T), and Uracil (in RNA)
  - **Purines:** Guanine and Adenine
  - **Pyrimidines:** Cytosine, Thymine, Uracil (in RNA)
- Each nucleotide is composed of a nitrogenous based with a 5-carbon sugar and a phosphate moiety (Fig 1)
- Hydrogen bonding occurs between homologous bases on adenine and thymine, and cytosine and guanine
- Adenine and Thymine share two hydrogen bonds while cytosine and guanine share **three** hydrogen bonds

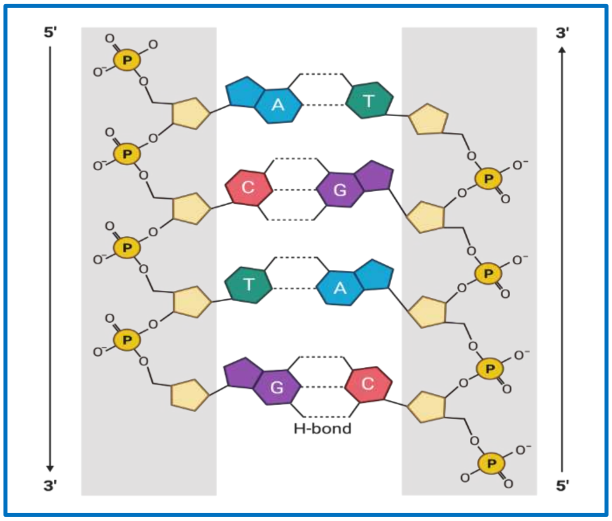

5'
3'
P
A
T
C
G
T
A
G
C
H-bond
3'
5'

Fig 1: Complementary nucleotide pairing and their structure.
Created by: Dr. Terrance Lynn, MD, using BioRender.com.

AMINO ACIDS AND THEIR STRUCTURES

- Amino acids are organic molecules that are composed of an amino acid (-NH3+), a carboxylic acid (-COOH), and an R-group (side chain)
  - Are present in both Dextrorotatory (D) and Levorotatory (L)
  - Natural amino acids are found in the L configuration (think L for "life")
- Can be classified into categories based on specific properties (Fig 2):
  - **Polar** neutral side chains: Serine and Threonine
  - **Amino** side chains: Asparagine and Glutamine
  - **Aliphatic** side chains: Valine, Alanine, Glycine, Isoleucine, Leucine, and Proline
  - **Sulfur-containing** side chains: Cysteine and Methionine
  - **Aromatic** side chains: Phenylalanine, Tryptophan, and Tyrosine
  - **Cationic** side chains: Histidine, Arginine, and Lysine
  - **Anionic** side chains: Glutamate and Aspartate

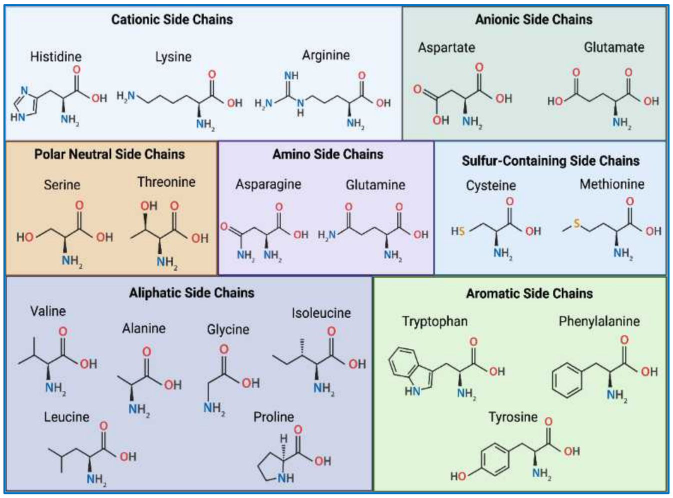

Cationic Side Chains
Histidine
Lysine
Arginine
Anionic Side Chains
Aspartate
Glutamate
Polar Neutral Side Chains
Serine
Threonine
Amino Side Chains
Asparagine
Glutamine
Sulfur-Containing Side Chains
Cysteine
Methionine
Aliphatic Side Chains
Valine
Alanine
Glycine
Isoleucine
Leucine
Proline
Aromatic Side Chains
Tryptophan
Phenylalanine
Tyrosine

Fig 2: Amino acids are classified by chemical properties.
Created by: Dr. Terrance Lynn, MD, using BioRender.com.

DEOXYRIBONUCLEIC ACID (DNA) AND RIBONUCLEIC ACID (RNA)

- Both DNA and RNA are large polymers with alternating 5-carbon sugars and phosphate groups
- Attachment of a nitrogenous base to a 3' or 5' carbon of sugar to create a **nucleoside**
- **DNA** is composed of two complementary strands of nucleotides (A, T, C, G) with a phosphate backbone
  - Sugars in DNA differ by the **lack** of a 2'-OH group
- **RNA** is **single-stranded** and is composed of the nucleotides Adenine, **Uracil**, Guanine, Cytosine
  - Sugars in RNA differ by the **presence** of a 2'-OH group
  - Two single strands can associate and form base pairs
  - Can form DNA-RNA duplexes under certain conditions
  - Types of RNA (Fig 3):
    - **Messenger RNA (mRNA):** composed of Exons (coding) and Introns (non-coding) after being translated from a DNA template. Introns are removed (spliced out) by exonucleases prior to translation
    - **Transfer RNA (tRNA):** Transfers amino acids to specific sites by a binding complementary sequence during translation (protein synthesis)
    - **Ribosomal RNA (rRNA)**: RNA portion of ribosome that is involved in the translation of RNA into polypeptides
  - **Ribozyme**: RNA molecule with enzymatic activity that catalyzes the reaction

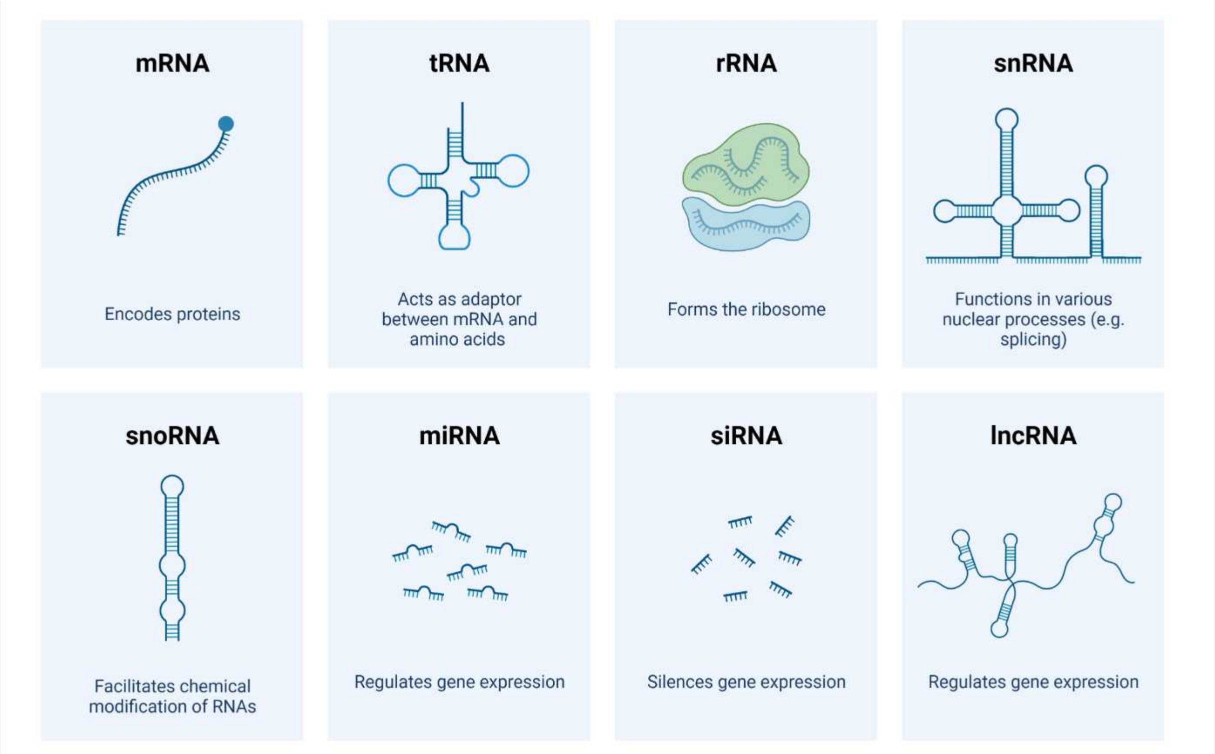

mRNA
Encodes proteins
tRNA
Acts as adaptor between mRNA and amino acids
rRNA
Forms the ribosome
snRNA
Functions in various nuclear processes (e.g. splicing)
snoRNA
Facilitates chemical modification of RNAs
miRNA
Regulates gene expression
siRNA
Silences gene expression
lncRNA
Regulates gene expression

Figure 3: Types of RNA. Created by: Dr. Akanksha Gupta, MD, using BioRender.com.

CHROMATIN AND STRUCTURE

- Chromatin is composed of DNA in a "packaged" state by coiling and supercoiling around histones (major chromatin-binding proteins) that exist in interphase
- **Euchromatin (Fig 4)**:
  - DNA in a loosely packed state which represents areas of active transcription and commonly occurs in interphase
  - In the G-band staining process, this will correspond to the "**light**" staining bands
- **Heterochromatin:**
  - DNA is in a tightly packed state, which represents areas of inactive transcription
  - In the G-band staining process, this will correspond to the "**dark**" staining bands

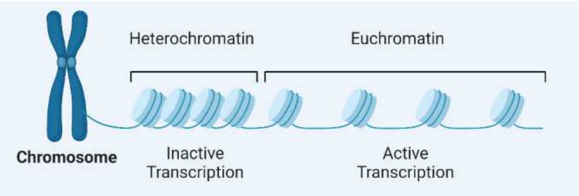

Heterochromatin
Euchromatin
Chromosome
Inactive Transcription
Active Transcription

Fig 4: Euchromatin and Heterochromatin.
Created by: Dr. Akanksha Gupta, MD, using BioRender.com.

- **Histones** H2A, H2B, H3, and H4 form octameric units for which dsDNA are coiled around and form the nucleosome

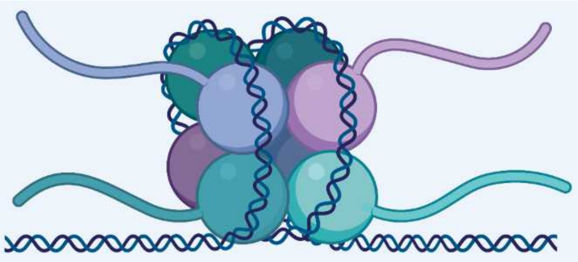


Fig 5: Nucleosome
Created by: Dr. Akanksha Gupta, MD, using BioRender.com.

- Nucleosomes (Fig 5) are connected to other nucleosomes by linker DNA
- **Nucleosomes** can be further compacted into 30-nm solenoid or spiral fibers containing 6 to 8 nucleosomes per turn
- Chromatin undergoes post-translational modifications (Fig 6)
  - **Methylation**:
    - Addition of -CH3 (methyl group) by methylases and can be removed by demethylases
    - Lysine is the classical amino acid that undergoes this type of post-translational modification
  - **Phosphorylation**:
    - Addition of $-PO_4$ to threonine, serine, or tyrosine by kinases and are removed by phosphorylases

  - **Acetylation**:
    - Addition of -CH_3CO by acetylases to lysine and can be removed by deacetylases
  - **Carboxylation**:
    - Addition of a -COOH group to glutamine by gamma-carboxylase
  - **Hydroxylation:**
    - Addition of an -OH group to proline, aspartate, and lysine
      - ◊ The common modification that occurs in collagen
  - **O-glycosylation:**
    - Addition of complex carbohydrates to hydroxyproline, serine, or threonine
  - **N-glycosylation:**
    - Addition of complex carbohydrates to asparagine

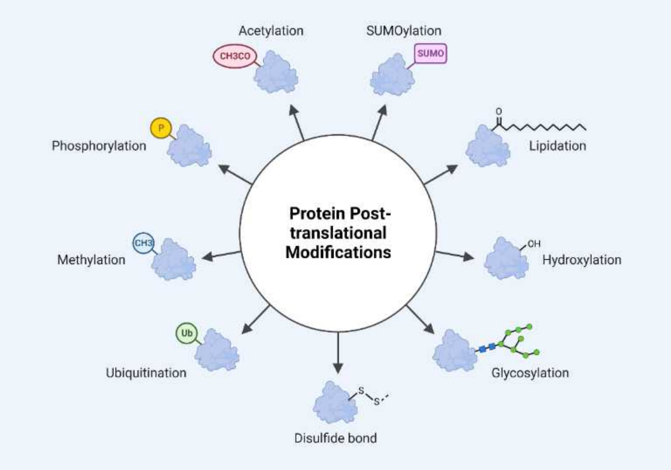

Acetylation
CH3CO
SUMOylation
SUMO
Phosphorylation
P
Lipidation
O
Protein Post-translational Modifications
Methylation
CH3
OH
Hydroxylation
Ub
Ubiquitination
Glycosylation
S
S
Disulfide bond

Fig 6: Post – translational modifications.
Created by: Dr. Akanksha Gupta, MD, using BioRender.com.

CHROMOSOMES AND CHROMOSOMAL STRUCTURE

- Chromosomes are **linear** dsDNA structures with associated proteins and are located in the nucleus
- Each chromosome has **two p-arms** (short arms) and **two q-arms** (long arms), a **centromere,** and **telomeres**
- **Centromere**:
  - The region in which the sister chromatids are joined and separate the p- and q-arms
  - In anaphase, the sister chromatids will split and attach to the mitotic spindle
- **Telomere**:
  - Heterochromatic DNA-protein complexes are found at the end of chromosomes and protect them from degradation or fusing to other chromosomes
- There are 22 chromosomes that are labeled 1 through 22 and are grouped by the location of the centromere (Fig 7)
  - **Metacentric**: Centromere is located in the middle
    - Chromosomes: 1, 3, 16, 19, 20
  - **Submetacentric**: Centromere located in a position such that chromosome p- and q-arms are unequal in size
    - Chromosomes: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, X
  - **Acrocentric**: Centromere is located near or at the end of the chromosome
    - Chromosomes: 13, 14, 15, 21, 22, Y
  - **Satellites**: Chromosomal segments separated by non-centromeric constrictions
    - Chromosomes: 21 and 22

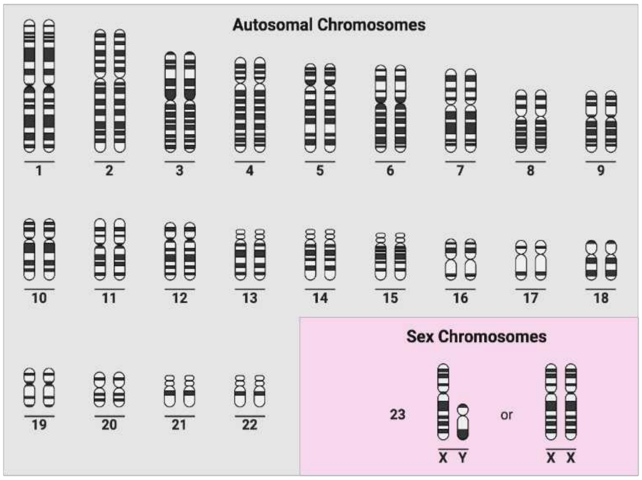

Autosomal Chromosomes
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Sex Chromosomes
23
X Y
or
X X

Fig 7: Chromosomes and their centromere location.
Created by Dr. Terrance Lynn, MD, using BioRender.com

- Chromosomal **number:**
  - **Ploidy**: refers to the number of homologous chromosome sets in a cell
    - **Haploid**: 1N → 23 chromosomes
    - **Diploid**: 2N → 46 chromosomes
  - **Polyploidy**:
    - Extra sets of chromosomes beyond haploid or diploidy
  - **Aneuploidy**:
    - An abnormal number of chromosomes in a cell
    - Can be loss or gain of chromosomes
      - ◊ **Monosomy**: an aneuploidy due to loss of a parental chromosome. Example: 45, XY, -8
      - ◊ **Trisomy**: an aneuploidy due to an addition of a parental chromosome. Example: 47, XXY, +18
  - **Mosaicism**:
    - Two or more cell lineages originating from the same zygote
  - **Chimera**:
    - Two or more cell lineages originate from different zygotes
  - Human genome is **diploid**:
    - 22 autosomal chromosomes and 2 sex chromosomes (XX, XY)
  - **Numerical abnormalities**:
    - Autosomal abnormalities are most often of a greater detriment than those in the sex chromosomes

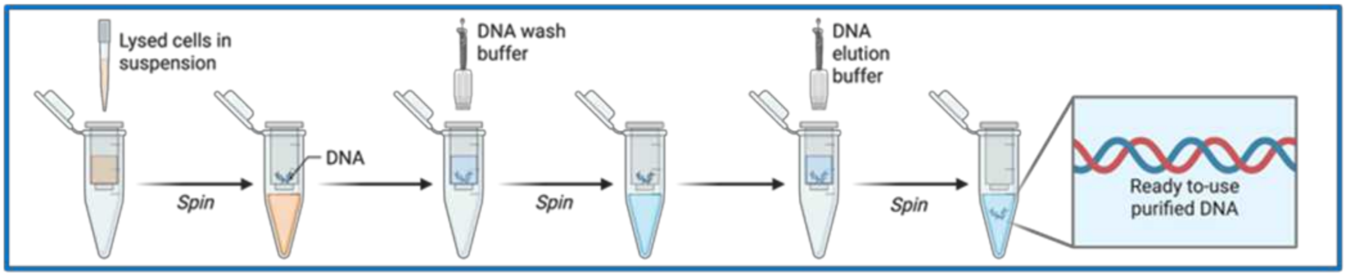


Fig 8: A Spin-Column, a form of solid-phase isolation of DNA. Created by Dr. Terrance Lynn, MD, using BioRender.com

NUCLEIC ACID EXTRACTION METHODS

- Nucleic acid can be extracted by many methods, including organic, inorganic, and solid-phase isolations
  - **Organic Isolation:**
    - Cells are suspended in solution
    - Cells are lysed to release DNA
    - Addition of **acetic acid and salt**, then spin specimen which will cause cell debris to pellet
    - The addition of **phenol and chloroform** will cause the extraction of DNA
    - Transfer eluate to a new tube and add ethanol to precipitate DNA
  - **Inorganic Isolation:**
    - Cells are suspended in solution
    - Cells are lysed with Tris, EDTA, and SDS
    - The addition of **sodium acetate** will cause protein precipitation to bottom of tube
    - Eluate is removed and placed into a new tube and isopropanol added
    - DNA will precipitate to bottom of tube as a pellet
  - **Solid-Phase Isolation** (Fig 8):
    - Cells are suspended in a solution
    - Cells then lysed by reagents in kit
    - Solution is then **acidified** using kit reagents which will cause cellular debris to precipitate
    - Silicate column is placed in new tube and eluate is placed into a column
    - DNA is then washed with buffer provided in kit
    - DNA is eluted through silicate column and is at bottom of tube
- The **yield** of DNA from specimens depends on the **cellularity** (based on the specimen type) as well as on the **assay**
  - **1 mL** of whole blood: up to **200 µg** of DNA
    - Assuming white count is 3-10 x 10^6/mL
  - **1 mL** of bone marrow: up to **500 µg** of DNA
  - **1 mg** of solid tissue: up to **10 µg** of DNA
  - **10 mL** of cytologic fluids (lavage, brushings, FNA): up to **250 µg** of DNA
  - **0.5 mL** of CSF: up to **5 µg** of DNA
  - **5-10x** scrolls of FFPE cut at 10µ: Up to **50 µg**

NUCLEIC ACID AMPLIFICATION METHODS

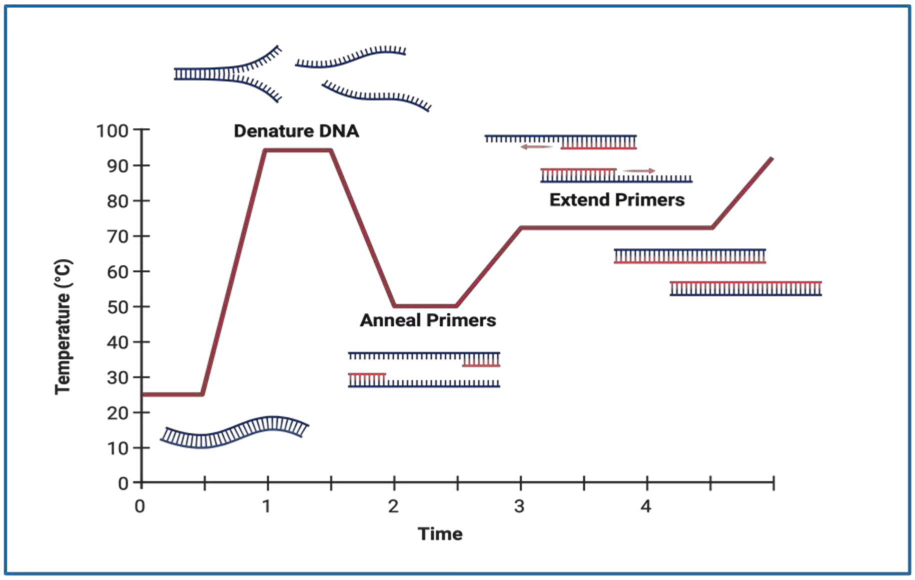


Fig 9: Process of polymerase chain reaction.

- There are many different types of amplification methods; we will focus mainly on basic methods
- **Polymerase chain reaction** (PCR) is a method in which a specific target/targets of DNA are amplified
- **Components** of PCR:
    - DNA template
    - Nucleotides
    - Oligonucleotide primers
    - Polymerase
    - Buffer solution, KCl, and $MgCl_2$ solution
- **Basic Steps** of Standard PCR (Fig 9):
    - **Denaturation** of DNA at **90-96ºC** for **20 to 60 seconds** will cause the DNA to become separate strands
    - **Annealing** of primers to the complementary sequences of the denatured template strand
        - Primers are designed to hybridize to the flanks of the region of interest
        - It occurs at a temperature of **50-70ºC** and lasts for up to **90 seconds**
    - **Extension** occurs when DNA polymerase catalyzes the addition of dNTPs to primers in which the template strand is used to synthesize a complementary strand
        - It occurs at a temperature of **68-75ºC** and lasts for up to **60 seconds**
    - **Each** cycle produces **2^n copies**

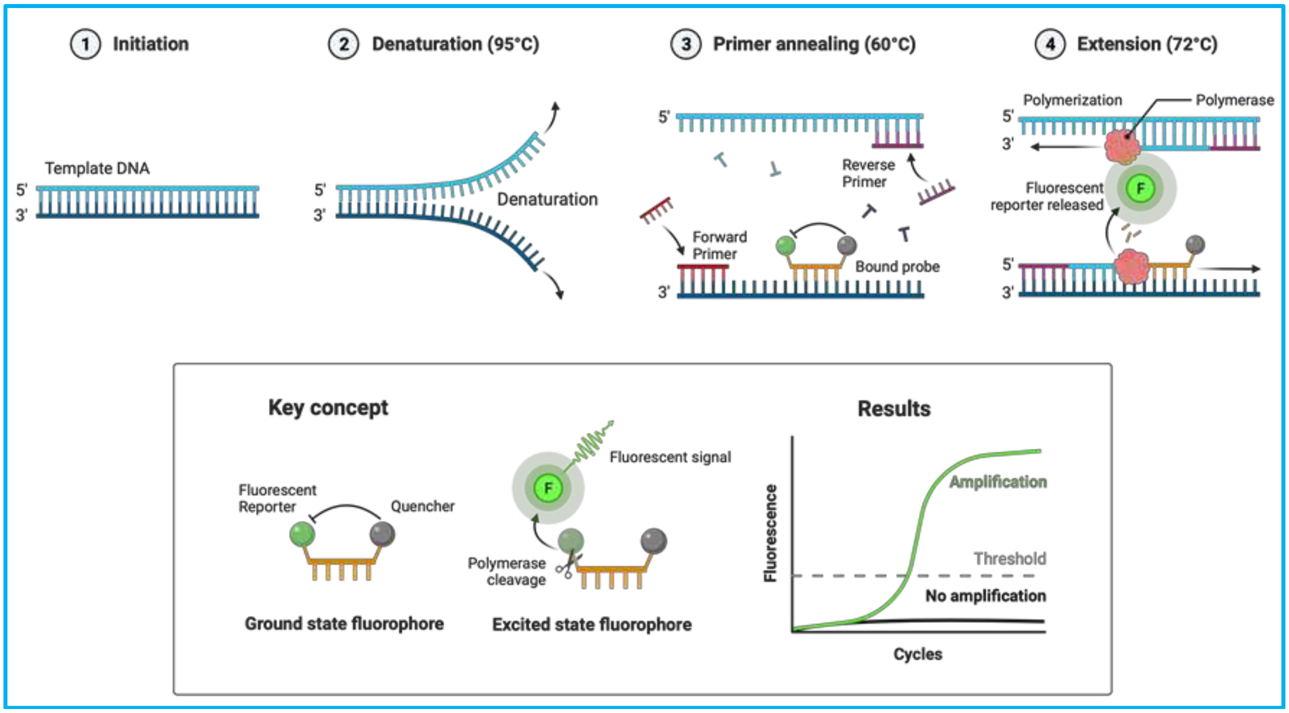

1 Initiation
2 Denaturation (95°C)
3 Primer annealing (60°C)
4 Extension (72°C)
Template DNA
5'
3'
Denaturation
Reverse Primer
Forward Primer
Bound probe
Polymerization
Polymerase
Fluorescent reporter released
F
Key concept
Fluorescent Reporter
Quencher
Fluorescent signal
Polymerase cleavage
Ground state fluorophore
Excited state fluorophore
Results
Fluorescence
Amplification
Threshold
No amplification
Cycles

Fig 10: Process of fluorescent based, quantitative polymerase chain reaction. Created by Dr. Terrance Lynn, MD, using BioRender.com

- **Quantitative PCR (Real-time PCR)** (Fig 10):
    - Similar to standard PCR and uses template DNA
    - DNA is denatured at 95ºC
    - Forward and reverse primers and probes bind to complementary sequences on denatured strands during annealing
    - **Probes** can either be **non-fluorescent** dye (EtBr) or **fluorescent** (SYBR Green)
        - SYBR Green has largely replaced EtBr due to its robust fluorescence and specificity, and low toxicity (compared to EtBr)
    - During extension, the fluorescent reporter probe is released after being cleaved by polymerase
    - Fluorescence is measured and a **Cycle Threshold (C_T)** is identified
        - **C_T** is the cycle in the fluorescence that surpasses the background level signal
        - Using standards, can plot **C_T** versus standard and get a numerical value for the **starting amount** of DNA in the sample

SEQUENCING METHODOLOGIES AND TECHNOLOGY

- **Sanger Sequencing (Chain Termination Method)** (Fig 11):
    - DNA template is placed into **4 separate tubes**; each tube contains its own primers, polymerases, and **deoxynucleotides** (either A, T, G, and C)

- Each tube then receives dideoxynucleotides (**ddNTPs**) that correspond to dNTPs
- The polymerase will randomly incorporate ddNTPs into the chain and synthesis is **terminated**
- DNA fragments are all variable in length and can either be separated by **size and length** through gel electrophoresis
- The **semi-automated method** uses a single tube with labeled ddNTPs with fluorophores. Fluorescence by the termination of chain with ddNTPs is detected with a laser and translated into a colored peak that corresponds to the DNA sequence

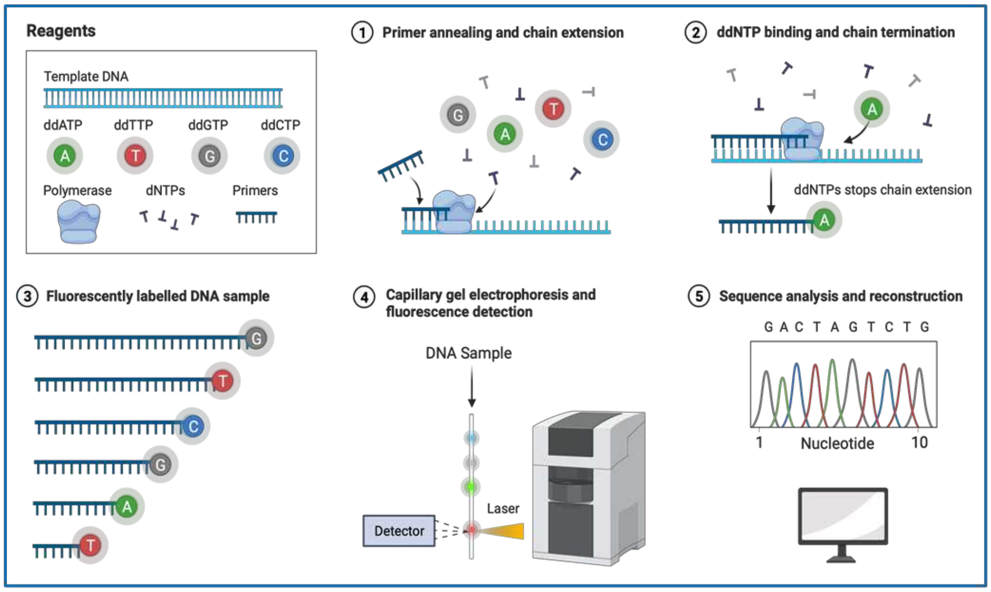

Reagents
Template DNA
ddATP
ddTTP
ddGTP
ddCTP
A
T
G
C
Polymerase
dNTPs
Primers
① Primer annealing and chain extension
G
A
T
C
② ddNTP binding and chain termination
A
ddNTPs stops chain extension
A
③ Fluorescently labelled DNA sample
G
T
C
G
A
T
④ Capillary gel electrophoresis and fluorescence detection
DNA Sample
Laser
Detector
⑤ Sequence analysis and reconstruction
G A C T A G T C T G
1
Nucleotide
10

Fig 11: Sanger sequencing and its output.

- **Pyrosequencing** (Fig 12):
  - Utilizes DNA synthesis for sequencing
  - **Steps**:
    - The single-stranded DNA template is incubated with enzymes and substrates
      - ◊ ATP sulfurylase, luciferase, apyrase, DNA polymerase, luciferin, and APS
      - ◊ Addition of dNTPs in a specific order
    - Pyrophosphate released from dNTP incorporation which is **converted to light** through **enzymes**
      - ◊ Pyrophosphate (PPi) + Sulfyrase → ATP
    - ATP + Luciferin → oxyluciferin + light
    - Light is detected → **Amount of light reflects** the **number of dNTPs** added
    - Apyrase removes any ATP or nucleotides before the next dNTP addition

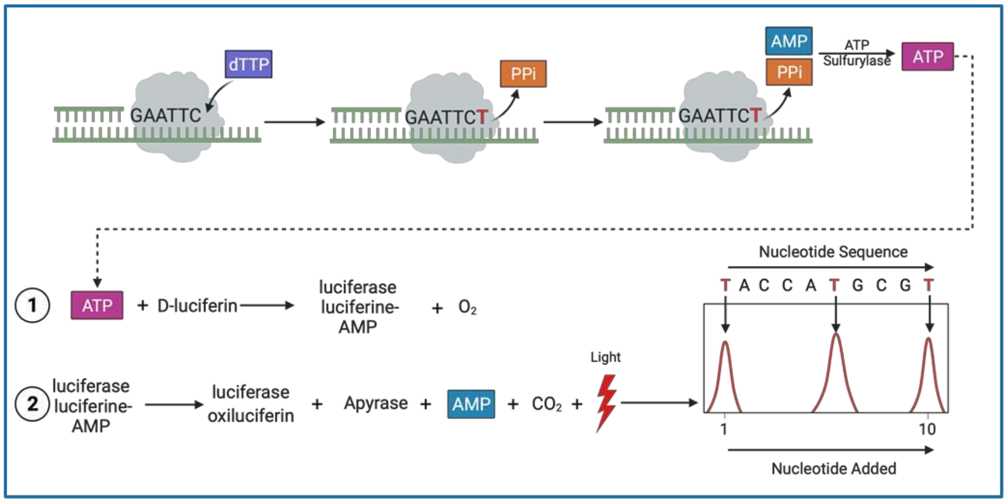

dTTP
GAATTC
PPi
GAATTCT
AMP
PPi
ATP
Sulfurylase
ATP
GAATTCT
1
ATP
+ D-luciferin
luciferase
luciferine-
AMP
+ O₂
2
luciferase
luciferine-
AMP
luciferase
oxiluciferin
+ Apyrase +
AMP
+ CO₂ +
Light
Nucleotide Sequence
T A C C A T G C G T
1
10
Nucleotide Added

Fig 12: Pyrosequencing methodology. Created by Dr. Terrance Lynn, MD, using BioRender.com

- **Next Generation Sequencing (Second Generation Sequencing)** (Fig 13):
  - Next-generation sequencing allows for **multiple specimens** and **targets** to be run at the **same time**
  - Each platform (manufacturer) has its own proprietary method for which sequencing is accomplished

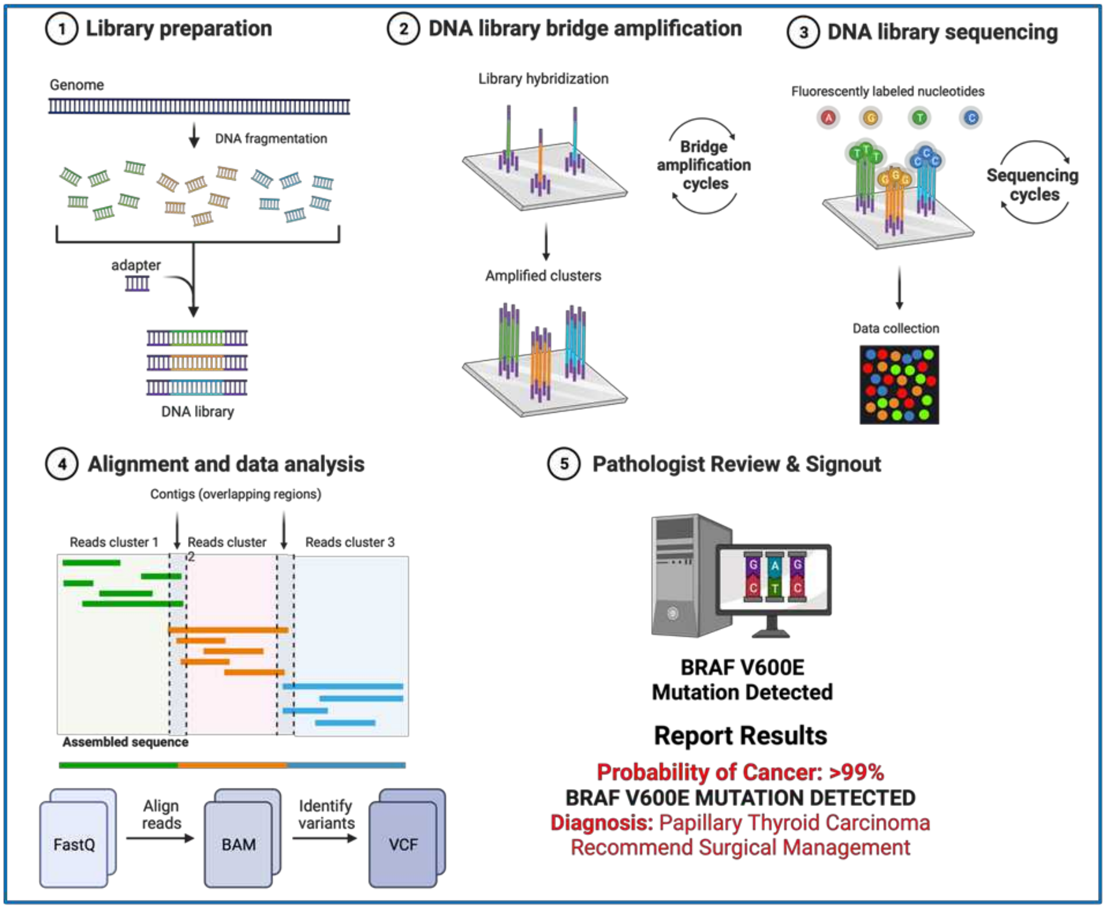
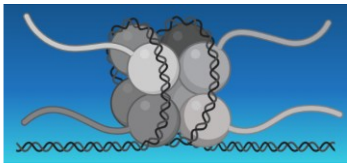
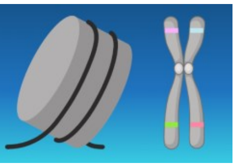

① Library preparation
Genome
DNA fragmentation
adapter
DNA library
② DNA library bridge amplification
Library hybridization
Bridge amplification cycles
Amplified clusters
③ DNA library sequencing
Fluorescently labeled nucleotides
A G T C
Sequencing cycles
Data collection
④ Alignment and data analysis
Contigs (overlapping regions)
Reads cluster 1
Reads cluster 2
Reads cluster 3
Assembled sequence
FastQ
Align reads
BAM
Identify variants
VCF
⑤ Pathologist Review & Signout
G A G
C T C
BRAF V600E Mutation Detected
Report Results
Probability of Cancer: >99%
BRAF V600E MUTATION DETECTED
Diagnosis: Papillary Thyroid Carcinoma
Recommend Surgical Management

Fig 13: Next generation sequencing workflow. Created by: Dr. Terrance Lynn, MD, using BioRender.com

  - **Library preparation:**
    - **Fragmentation** of DNA sample (physical or enzymatic)
    - Polymerase chain reaction to generate **amplicons**
    - **Adapter** sequence **ligation** to both a 5' and 3'-ends of fragment
    - **Size selection** to optimize sequence quality and efficiency
    - **Quantification** of final library and quality control
      - The **output** will only be as **good** as **this step** due to the **quality** of the library
  - **Clonal amplification:**
    - Multiple DNA libraries are pooled into the same run and sequenced at the same time due to **barcoding** (addition of known sequences per patient)
    - Amplification occurs in a **3D space** (per platform specifics)
    - Amplification and sequencing can occur all at the **same time**
    - Data generated is processed and **base calling** occurs → sequence reads
  - **Sequence Analysis:**
    - Sequences are aligned with a **known reference** sequence
    - **Bioinformatic pathway** generates requisite formats
      - **FASTQ File**: It is a text list of unaligned reads that contains 4 lines of text per sequence, its corresponding sequence identifier, and a quality score
      - **BAM:** binary file format → a storage format for reads
      - **VCF**: Variant call format → a format in which sequence variants are annotated
  - **Read Depth ("Coverage"):**
    - Number of reads that **overlap** with alignment at a specific locus of interest
    - Often expressed as a **%**
  - **Variant allele frequency (VAF):**





    - A measurement (in %) of the sequencing reads observed, that match a **specific variant** in DNA divided by the coverage at a specific locus
    - Essentially a surrogate marker for the **amount of DNA** in original sample that contains variant
    - In **diploid zygosity**:
      - ◊ **Heterozygous** loci should have approximately 50% VAF
    - **Homozygous** loci should have nearly 100% VAF
    - **Reference** loci should be near or at 0%
    - If any of the above are not close to these values → consider **incorrect** base calling or errors with alignment
  - **Strand Bias (SB):**
    - Measurement of how much variant reads **deviate** from the likelihood of sequencing plus and minus strands
    - A high SB is more indicative of an **alignment process artifact** than an actual true mutation
  - **Variant quality (QUAL) scores:**
    - QUAL scores are generated during the calling of variants step
    - QUAL scores transformed into log scaled values (**PHRED**)
    - QUAL values vary between assays, methods of capture, and variant calling software
    - Laboratories should independently assess the performance of each assay
  - **Interpretation and creation of report** in the context of cytomorphology & clinical
    - VAF and tumor cellularity are critical considerations
    - If VAF **>>** than expected → consider **germline** variant or **loss** of heterozygosity
    - If VAF **<<** than expected → consider **low** tumor heterogeneity or **false positive**
  - Writing a molecular report requires knowledge of various reporting systems and the use of appropriate terminology
    - The following is the best practice for writing or understanding a molecular genetic test report
    - Gene names are reported as defined by the **HUGO** Gene **Nomenclature** Committee
    - **Copy number variations** (CNVs) should be clearly defined and includes "**gain**" or "**loss**" terms
    - **Single nucleotide variations** (SNVs) and insertion-deletions should be reported in the **p**. and **c.** formats
    - **Protein level** ("p.") amino acid sequences
    - **Coding DNA** ("c.") reference sequences
    - Insertion-deletion is often referred to as the shortened name "**indels**"
    - The **transcript reference sequence** should also be reported
    - Transcript reference sequences are written in the "**NM_000000.0**" format
  - There is a specific classification scheme of variants that is continuously updated based on new research and information
  - American College of Medical Genetics and Genomics (ACMG) and Association of Molecular Pathology (ACMG-AMP System) is a variant classification system
    - There are **5 tiers of classification:**
      - ◊ Benign
      - ◊ Likely benign
      - ◊ Variant of unknown significance
      - ◊ Likely pathogenic
      - ◊ Pathogenic
  - For somatic mutations, FDA standards and guidelines have an evidence-based categorization system which is based on the diagnosis, prognosis, and potential therapeutics
    - **Tier I:** Variants of Strong Clinical Significance (Therapeutic, prognostic, and diagnostic)
      - ◊ Level A evidence: FDA-approved therapy exists
      - ◊ Level B evidence: Well-powered studies with expert consensus
    - **Tier II:** Variants of Potential Clinical Significance (Therapeutic, prognostic, and diagnostic)
      - ◊ Level C evidence: FDA-approved therapy for alternative tumor types or investigational therapies; Multiple small, published studies with some consensus
      - ◊ Level D evidence: Preclinical trials or few case reports, no consensus
    - **Tier III:** Variants of Unknown Clinical Significance
      - ◊ Not observed at significant allele frequency in general or subpopulation database, or cancer database
      - ◊ No convincing published data/evidence of cancer association
    - **Tier IV:** Benign or Likely Benign Variants
      - ◊ Observed at a significant allele frequency in general or subpopulation database
      - ◊ No existing evidence or published association of cancer
  - Reporting of these tiers varies among laboratories as many opt to only **report Tier I and II**; other labs will include Tier III periodically
    - Reports should be informative but concise
    - Molecular testing reports are "static" meaning no changes are made even in the setting of new associations or changes to variant listing in the tiers
- Reporting many Tier III results could reduce the conciseness of the report and lead to an overwhelming report for the clinician → use best judgment and caution when choosing to report Tier III findings

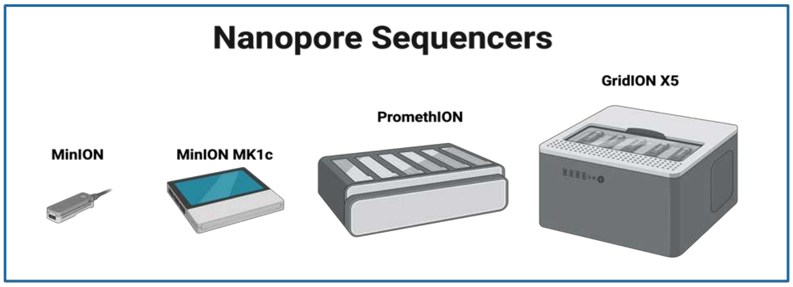

Nanopore Sequencers
MinION
MinION MK1c
PromethION
GridION X5

Fig 14: Nanopore sequencing instrumentation currently available. Created by: Dr. Terrance Lynn, MD, using BioRender.com

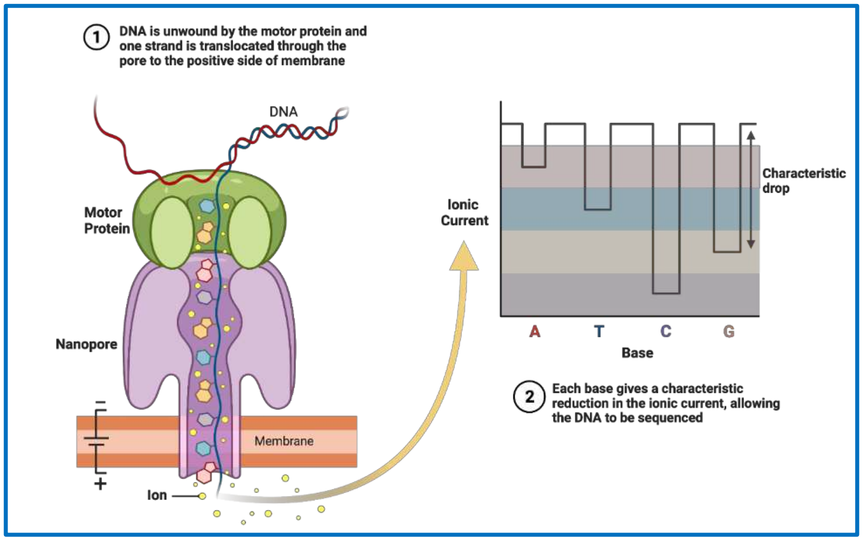

① DNA is unwound by the motor protein and one strand is translocated through the pore to the positive side of membrane
DNA
Motor Protein
Nanopore
Membrane
−
+
Ion
Ionic Current
Characteristic drop
A
T
C
G
Base
② Each base gives a characteristic reduction in the ionic current, allowing the DNA to be sequenced

Fig 15: Nanopore sequencing methodology and how it functions.

- **Third Generation Sequencing (Nanopore Sequencing)** (Fig 14 and 15):
  - Largely still for **research** use only
  - The benefit to this new technology is that the clinical amplification step is **bypassed**, unlike that of second-generation sequencing
  - This is a **faster** method in which the preparation of the genetic material (DNA, RNA) is shortened
  - Allows for **longer read lengths** on average when compared to second-generation sequencing
  - Recently, nanopore sequencing has become instrumental in recent years of the COVID-19 pandemic due to the need for fast identification of variants
  - **Nanopore sequencing**:
    - Utilizes a **single chip** that is permeated with many protein nanopores
    - These **protein nanopores** have an electrically resistant polymer membrane for which an electric charge is applied, and a known current is present at baseline dsDNA is met with a denaturing enzyme which then allows ssDNA to flow through protein nanopore
    - As each base cross through the protein nanopore, the changes in current allow for identification of the base (and sequence)

CYTOGENETIC EXAMINATION

- Requires **living cells** (specific cell depends on interest) to grown in culture
  - Blasts, progenitor cells, and malignant cells
    - Can autonomously divide, do not need interleukins or chemical added to stimulate and cause cells to replicate
  - Plasma cells, B-cells, and T-cells that are terminally differentiated
    - Requires **addition of interleukins** or others to **stimulate** cells to divide
- When culture is ready, **colchicine** is added to the plate
  - Causes a **metaphase arrest** of the cells due to inhibition of the mitotic spindle
- Hypotonic solutions are added which cause the chromosomes to spread out due to cellular swelling
- A **modified Carnoy** solution is added to the cells to fix them
  - Modified Carnoy solution → 3:1 mixture of ethanol to glacial acetic acid

- Cells are placed on a slide and then stained with **Giemsa**
  - The staining process is called “**G-banding**”
- Bands are visible after staining
  - Resolution is variable depending on the purpose
    - The complete karyotype has **450 bands** → each band is about 6 Mb of DNA
  - The maximum visual resolution on a karyotype is between 5 and 10 Mb
- Requires **at least 20** cells of interest in **metaphase** that are examined under light microscopy
- **Clinical utility** of Cytogenetics:
  - Diagnosis
  - Prognosis
  - Identification of residual disease
  - Identification of clonal evolution (i.e., MDS with additional cytogenetic abnormalities)

FLUORESCENT IN SITU HYBRIDIZATION (FISH)

- Different from chromosomal analysis using cytogenetics because cells are in **interphase**
  - Useful for **FFPE tissue** samples
  - **Cytologic** specimens (i.e., fixed slides, touch preps, and cytospins)
- **Basic steps** of FISH (Fig 16):
  - Slides containing cells of interest are dehydrated with a series of ethanol washes

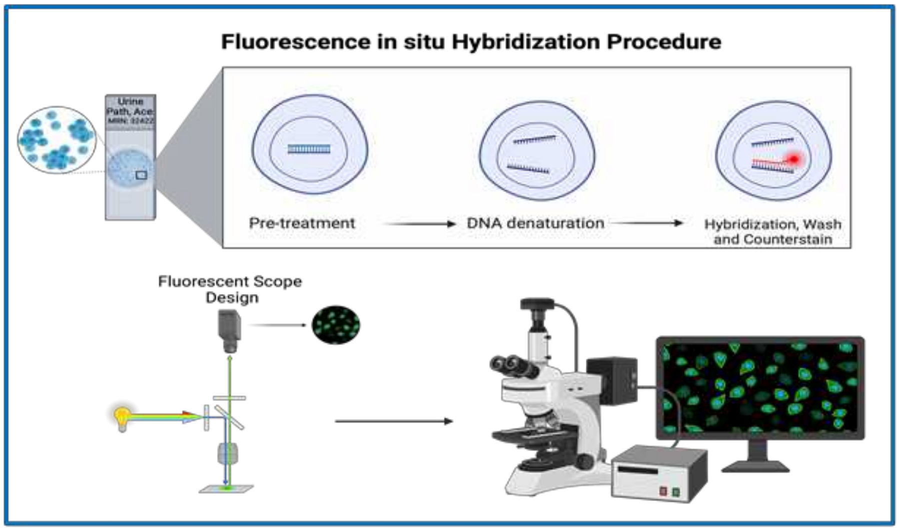

Fluorescence in situ Hybridization Procedure
Urine Path, Ace MRN: 32422
Pre-treatment
DNA denaturation
Hybridization, Wash and Counterstain
Fluorescent Scope Design

Fig 16: Equipment to interpret FISH studies. Created by Dr. Terrance Lynn, MD, using BioRender.com

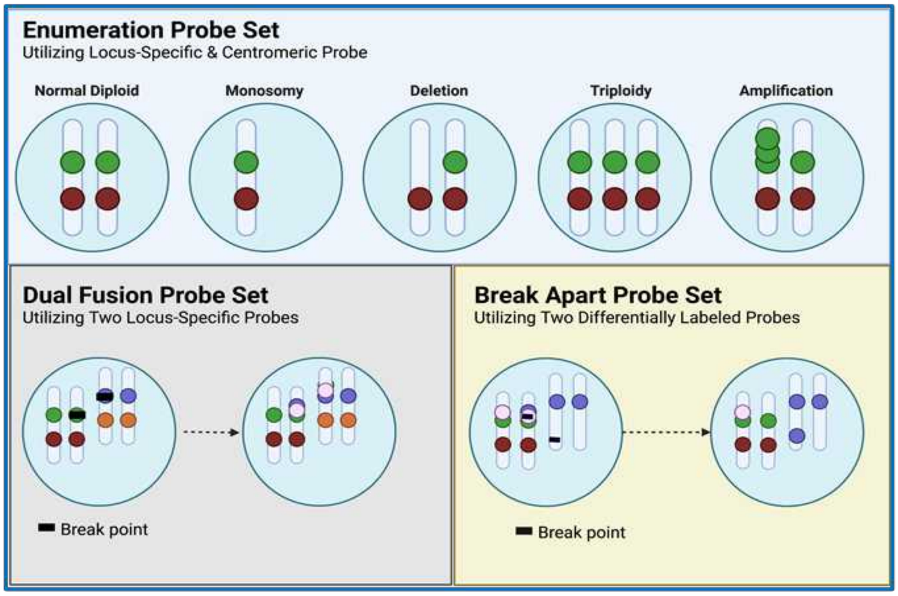

Enumeration Probe Set
Utilizing Locus-Specific & Centromeric Probe
Normal Diploid
Monosomy
Deletion
Triploidy
Amplification
Dual Fusion Probe Set
Utilizing Two Locus-Specific Probes
Break point
Break Apart Probe Set
Utilizing Two Differentially Labeled Probes
Break point

Fig 17: FISH showing various probe sets.

- **Co-denaturation** and **hybridization**
    - Fluorescent-labeled probe specific to the target of interest is then added
    - The slide is incubated for approximately 20 hours to denature dsDNA
    - Over this time period, the probe hybridizes with the target sequence
  - The slide is washed to remove excess probe
  - **DAPI counterstain** is applied
  - A mounting medium is then applied, and a coverslip added
- **Types of probes** are selected based on the number of genes involved (Fig 17). These probes can be:
  - **Break-apart probe:**
    - A **single** gene is involved in the translocation
    - If **both** red and green colors are seen → translocation is **present**
  - **Dual-color, dual-fusion probe:**
    - **Two genes** are involved in the translocation and are **known**
    - One gene is flanked by a red probe; the other gene is flanked by a green probe
    - If **yellow** color is seen → translocation is **present** (yellow color is caused by red and green being immediately adjacent/"fused" to each other)
    - If **both** red and green colors are seen → translocation is **absent**
- **Clinical utility** of FISH:
  - Diagnosis
  - Prognosis
  - Detection of residual disease
  - Identification of fetal aneuploid

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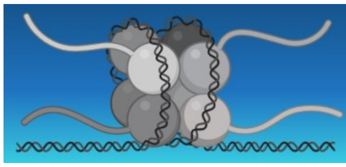
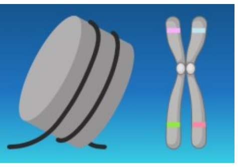


18. MOLECULAR PATHOLOGY



MOLECULAR TESTING IN MALIGNANT MELANOMA FOR TARGETED THERAPY

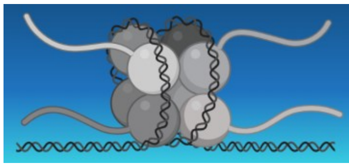
Gene	Mutation	Clinical Information	Targeted therapy or Therapeuti Decision	Methods of Detection
BRAF	Mutations in codon 600 →V600E, V600K	If present, tumor may be sensitive to **targeted therapies** (*BRAF*, *MEK* inhibitors)	Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, binimetinib	NGS, Sanger, Pyrosequencing, PCR
KIT	Exon 11 and 13: Codons W557, V559, L576, K642	If present, tumor may be sensitive to ***KIT* inhibitor**	Imatinib, nilotinib	NGS, Sanger, Pyrosequencing, PCR
	Exon 17: D816H	Associated with **resistance** to *KIT* inhibitors	Not eligible for Imatinib, nilotinib	NGS, Sanger, Pyrosequencing, PCR
	Amplification	Associated with **resistance** to *KIT* inhibitors	Not eligible for Imatinib, nilotinib	NGS, Sanger, Pyrosequencing, PCR
NRAS	Mutations in Codon 12, 13, 61	Indicates poor patient survival but patients may have response to **MEK inhibitors**	No targeted therapy at this time	NGS, Sanger, Pyrosequencing, PCR
PDGFRA	Exon 12, 14, 18 variants	Most commonly detected in mucosal and acral melanomas; may benefit from **TKI therapy**	May benefit from Imatinib and Crenolanib	NGS, Sanger

MOLECULAR TESTING IN BREAST CANCER FOR TARGETED THERAPY

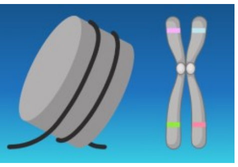
Gene	Mutation	Clinical Information	Targeted therapy or Therapeutic Decision	Methods of Detection
ER	-------	Prognostic and therapeutic information	Anti-estrogen agents	IHC, NGS
PR	-------	Prognostic and therapeutic information	Anti-estrogen agents	IHC, NGS
ERBB2 (HER2)	Amplification; S310, L755	If amplified, eligible for **targeted** therapy	Trastuzumab	IHC, NGS
PIK3CA	E542, E545, or H1045	If mutated, eligible for **targeted** therapy	Alpelisib	NGS

MOLECULAR TESTING IN COLORECTAL CANCER FOR TARGETED THERAPY

Gene	Mutation	Clinical Information	Targeted therapy or Therapeutic Decision	Methods of Detection
MSI/MMR	Loss of *MLH1, PMS2, MSH2, MSH6*	If loss of *MLH1* in elderly, consider *MLH1* promoter methylation; if young and loss of any *MLH1, PMS2, MSH2, MSH6*, **screen** for **Lynch Syndrome**	No	IHC (most common), NGS, PCR
	MSI-High	Confers a **better** prognosis	No benefit from 5-fU; can consider other agents	
BRAF	V600E, V600K	If present, most likely **sporadic** tumor rather than syndromic but does **NOT** exclude Lynch; Can consider anti-*EGFR* agents in addition to *BRAF* inhibitor; provides prognostic information	Encorafenib, +/- Cetuximab	NGS, Sanger, Pyrosequencing, PCR
KRAS	Exon 2: Codon 12, 13; Exon 3: Codons 59, 61; Exon 4: Codon 117, 146	Perform on all patients with **metastatic** colorectal cancer; Can consider anti-*EGFR* agents; Significant progression free survival if adding anti-*EGFR* agent in patients with wild-type *KRAS* mutations compared to only chemotherapy	Not eligible for Cetuximab or Panitumumab	NGS, Sanger, Pyrosequencing, PCR
NRAS	Exon 2: Codon 12, 13; Exon 3: Codons 59, 61; Exon 4: Codon 117, 146	Perform on all patients with **metastatic** colorectal cancer; Can consider anti-*EGFR* agents; Significant progression free survival if adding anti-*EGFR* agent in patients with wild-type *KRAS* mutations compared to only chemotherapy	Not eligible for Cetuximab or Panitumumab	NGS, Sanger, Pyrosequencing, PCR
NTRK	Fusions	If mutated, eligible for **targeted** therapeutic agent	Loratrectinib	NGS, FISH, IHC, pyrosequencing, PCR
MLH1 **Promoter Methylation**	Methylation of *MLH1* Promoter	If no *BRAF, KRAS, NRAS* mutations detected and demonstrate loss on *MLH1* IHC, perform testing	If *MLH1* expression loss and promoter methylation → sporadic	Methylation Assay



18. MOLECULAR PATHOLOGY



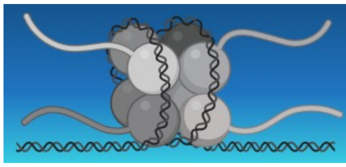
MOLECULAR TESTING IN LUNG CANCER FOR TARGETED THERAPY

(Testing is appropriate on adenocarcinomas, large cell, and non-small cell lung carcinomas (NSCLC), +/- Squamous cell carcinomas)

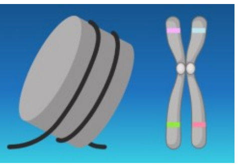
Gene	Mutation	Clinical Information	Targeted therapy available for mutation	Methods of Detection
EGFR	Exons 18-21, L858R, exon19 deletion	**Rare** in squamous cell carcinoma (SCC); if present in SCC, consider adenosquamous; Indicates clinical utility for TKI	Erlotinib, Afatinib, Gefitinib, Osimertinib, Dacomitinib	NGS (preferred), PCR
	Exons 20 insertion	Resistance to certain TKI, choose alternate TKI	Amivantamab, Mobocertinib	
	T790M	Resistance to certain TKI, choose alternate TKI	Osimertinib	
ALK	Rearrangement	About 5% of NSCLC cases will have this alteration; often in **young non-smokers with adenocarcinoma**	Crizotinib, Certinib, Alectinib, Brigatinib, Lorlatinib	NGS, FISH, RT-PCR, IHC (screening)
ROS1	Rearrangement	**Rare**, only ~1% will have rearrangement, patients who lack *ALK*, *KRAS*, and *EGFR* mutations more likely to have	Crizotinib, Certinib, Lorlatinib, Entrectinib	NGS, FISH, IHC (screening, few labs have), RT-PCR
BRAF	p.V600E	~4% of patients will have mutation but comprises ~50% of all *BRAF* mutations; if mixed histology, may have	Dabrafenib, Trametinib	NGS, PCR, IHC, Sanger
KRAS	Codons 12, 13, 61, 146	If *KRAS* G12C mutated, often resistant to other therapies (EGFR inhibitors)	Sotorasib	NGS, PCR
MET	Exon 14 skipping variants	Uncommon	Tepotinib, Capmatinib	NGS
	High-level amplifications	Occur in about 4% of cases; Patients who developed resistance to EGFR-TKIs	Literature demonstrates benefit with Crizotinib	NGS, FISH
NTRK1/2/3	Rearrangements	*NTRK1* **fusions** common; others are rare	Entrectinib, Larotrectinib	NGS, FISH, RT-PCR, IHC
PD-L1	------	No standardized interpretation guideline	Atezolizumab, Nivolumab, Pembrolizumab	IHC

MOLECULAR TESTING IN THE CENTRAL NERVOUS SYSTEM

Gene	Mutation	Clinical Information	Targeted therapy	Methods of Detection
IDH1	Codon R132	Seen in Glioblastoma, astrocytoma, and oligodendroglioma, Associated wit **improved** prognosis (if with homozygous *CDNK2A* deletion →bad)	No targeted therapy at this time	NGS, PCR, Sanger, Pyrosequencing
IDH2	Codon R140, R170	Seen in Glioblastoma, astrocytoma, and oligodendroglioma, Associated with **improved** prognosis (if occurs with homozygous *CDNK2A* deletion →bad)	No targeted therapy at this time	NGS, PCR, Sanger, Pyrosequencing
ATRX	Loss of function	Often seen in cases with *IDH1*/2 mutations; not seen in cases that have a 1p/19q co-deletion (mutually exclusive	No targeted therapy at this time	NGS, IHC, Sanger, Pyrosequencing
1p/19q co-deletion	Deletion	Seen in Oligodendroglioma; Associated with a positive prognosis	No targeted therapy at this time	NGS, FISH
TERT	Mutation in Promoter	Present in majority of oligodendrogliomas; Associated with an unfavorable prognosis in astrocytomas (with wild-type *IDH*)	No targeted therapy at this time	NGS, PCR, Sanger, Pyrosequencing
MGMT	Promoter methylation	If present, indicates response to targeted therapy; if absent, Temozolomide is not useful	**Temozolomide**	Methylation-specific PCR
BRAF	Codon V600 mutations	Seen in pilocytic astrocytomas, gangliogliomas, and pleomorphic xanthoastrocytoma; Activating mutations are often targetable; *BRAF*-KIAA1549 is a diagnostic truncated fusion, not a therapy defining fusion	May consider BRAF and MEK inhibitors	NGS, PCR, Sanger, Pyrosequencing, IHC
H3F3A, HIST1H3B	Codon K27, G34 mutations	Observed in H3K27M-mutant gliomas (Diffuse midline glioma, pediatric cortical gliomas)	No targeted therapy at this time	NGS, PCR, Sanger, Pyrosequencing, IHC
RELA	Fusions	Seen in some supratentorial ependymomas (*RELA*-Fusion positive); associated with **aggressive** behavior	No targeted therapy at this time	RT-PCR, FISH
EGFR	Amplifications	*IDH*-wild type astrocytomas that are histologic grade 2, or 3 has any of these genetic alterations: ***TERT* promoter, *EGFR* amplification, or a combined gain of chromosome 7 or loss of chromosome 10, the tumor is classified as a Glioblastoma**	No targeted therapy at this time	NGS, FISH
Chr 7	Gain of Chr 7			
Chr 10	Loss of Chr 10			



18. MOLECULAR PATHOLOGY



MOLECULAR TESTING IN ADIPOCYTIC TUMORS

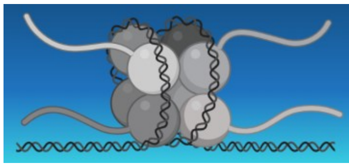
Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Lipoblastoma	*PLAG1*	8q11	Rearrangements	NGS, FISH
Lipoma	*HMGA2/HMGA1*	12q13-q15; 6p21	Fusions	NGS, FISH
Angiolipoma	*PRKD2*	19q13	Activating mutations	NGS, FISH
Spindle cell/pleomorphic lipoma	*RB1*	Monosomy or partial loss of 13, 16	Deletion/Loss	NGS, FISH
Chondroid lipoma	*C11orf95-MKL2*	t(11;16)(q13;p12-13)	Fusion	NGS, FISH
Hibernoma	*MEN1, AIP*	11q13-21	Deletion/Loss; rearrangements	FISH
Atypical lipomatous tumor/Well-differentiated liposarcoma	*MDM2*	12q12-21	Amplification	NGS, FISH
Dedifferentiated or Undifferentiated liposarcoma	*MDM2*	12q14	Amplification	NGS, FISH
Myxoid/Round cell liposarcoma	*FUS-DDIT3*	t(12;16)(q13;p11)	Fusions	NGS, FISH
	EWSR1-DDIT3	t(12;22)(q13;p11)	Fusions	NGS, FISH

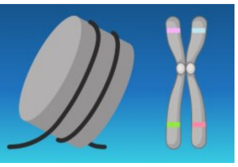
MOLECULAR TESTING IN SKELETAL AND SMOOTH MUSCLE TUMORS

Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Alveolar rhabdomyosarcoma	*PAX3-FOXO1* (~80% of cases)	t(2;13)(q35;q14)	Fusions	NGS, FISH
	PAX7-FOXO1 (~20% of cases)	t(1;13)(p36;q14):	Fusions	NGS, FISH
Spindle cell/sclerosing rhabdomyosarcoma	*VGLL2, NCOA2*	---	Sequence variant	NGS, FISH
	MYOD1	----	Fusions	NGS
Embryonal rhabdomyosarcoma	*KRAS, NRAS, HRAS, FGFR4*	----	Activating sequence variants	NGS

MOLECULAR TESTING IN MYOFIBROBLASTIC AND FIBROBLASTIC TUMORS

Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Inflammatory myo-fibroblastic tumor	*ALK* *(Many partners)*	2p23	Fusions	NGS, FISH
Infantile fibrosarcoma	*ETV6-NTRK3*	t(12;15)(p13;q26	Fusions	NGS, FISH
Low-grade fibromyxoid sarcoma (LGFMS)	*FUS-CREB3L2* (90% cases)	(7;16)(q32-34;p11)	Fusions	NGS, FISH
	FUS-CREB3L1	t(11;16)(p11;p11)	Fusions	NGS, FISH
Sclerosing epithelioid fibrosarcoma (SEF)	*EWSR1-CREB3L1*	t(7;16)	Fusions	NGS, FISH
Tenosynovial giant cell tumor	*CSF1*	1p13	Rearrangements	NGS, FISH
Deep benign fibrous histiocytoma	*PRKCB, PRKCD*	16p12.2-p12.1 3p21.1	Fusions	NGS, FISH
Desmoid-type fibromatosis	*CTNNB1* (sporadic)	3p22.1	Mutations (activating)	NGS
	APC (FAP-related)	5q22.2	Mutations (LOF)	NGS
Giant cell fibroblastoma	*COL1A1-PDGFB*	t(17,22)(q22;q13)	Fusions	NGS, FISH
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB*	t(17;22)(q22;q13)	Fusions	NGS, FISH
Nodular fasciitis	*USP6-MYH*	t(17;22)(p13;q12)	Fusions	NGS, FISH
Fibrous hamartoma of infancy	*EGFR*	Rarely t(2;3)	Exon 20 insertions/duplications	NGS, PCR
Desmoplastic fibroblastoma	*FOSL1*	t(2;11)(q31;q12) or 11q12	Rearrangements	FISH
Myofibroblastoma	*RB1*	13q14	Deletion/Loss	NGS, FISH
Cellular angiofibroma	*RB1*	13q14	Deletion/Loss	NGS, FISH





Superficial acral fibromyxoma	*RB1*	13q14	Deletion/Loss	NGS, FISH
Calcifying aponeurotic fibroma	*FN1-EGF*	ins(2;4)	Fusions	NGS
Angiofibroma of soft tissue	*AHRR-NCOA2*	t(5;8)(p15;q13)	Fusion	NGS
Solitary fibrous tumor	*NAB2-STAT6*	12q13	Fusion	NGS, IHC

MOLECULAR TESTING IN VASCULAR AND PERIVASCULAR TUMORS

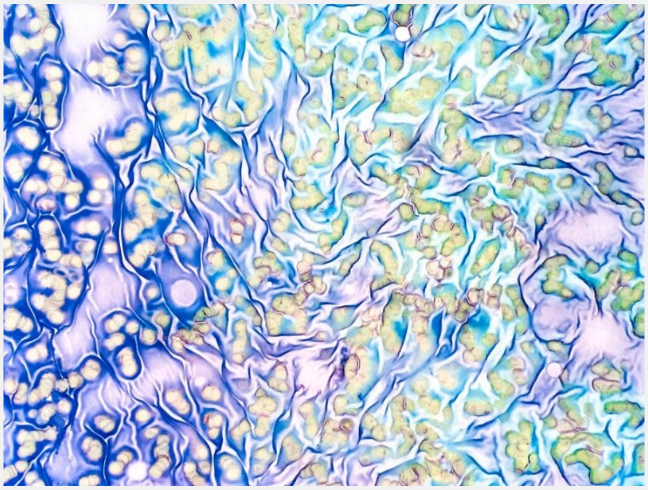
Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Epithelioid hemangioma	*FOS, FOSB*	----	Fusions	NGS, FISH
Epithelioid hemangioendothelioma	*WWTR-CAMTA1*	*CAMTA1* → 1p36.23 *WWTR1* → 3q25.1	Fusion	NGS, IHC, RT-PCR
	YAP-TFE3	*YAP1* Exon1 to *TFE3* Exon 4	Fusion	NGS, RT-PCR
Myopericytoma/myofibroma	*PDGFRB*	----	Mutations	NGS
Glomus tumor	*SRF-RELA*	----	Fusions	NGS, FISH
	NOTCH	----	Mutation	NGS
	BRAF, KRAS	----	Mutation	NGS

MOLECULAR TESTING IN BONE AND CARTILAGE TUMORS

Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Mesenchymal Chondrosarcoma	*HEY1-NCOA2*	t(8;8)(q13;q21)	Fusion	NGS, FISH
Chondroblastoma	*H3F3A K36M*	----	Variant	NGS
Aneurysmal Bone Cyst	*USP6*	17p13.2	Fusions (multiple partners)	NGS, FISH
Giant Cell Tumor of Bone	H3F3A G34W, G34L	----	Variant	NGS

MOLECULAR TESTING IN ROUND BLUE CELL & MISCELLANEOUS TUMOR

Diagnosis	Gene	Chromosomal location	Type of Mutation	Method of Detection
Desmoplastic Small Round Cell Tumor	*EWSR1-WT1*	t(11;22)(p13;q12)	Fusions	NGS, FISH
Ewing Sarcoma	*EWSR1-FLI1*	t(11;22)(q24;q12)	Fusions	NGS, FISH
	EWSR1-ERG	t(21;22)(q22;q12)	Fusion	NGS, FISH
Ewing-Like Sarcoma	*CIC-DUX4*	t(4;19) or t(10;19)	Fusions	NGS
	BCOR-CCNB3	t(X;X)	Fusion	NGS
Alveolar Soft Part Sarcoma	*ASPSCR1-TFE3*	t(X;17)	Fusions	NGS, FISH, RT-PCR
Angiomatoid Fibrous Histiocytoma	*ATF1/FUS*	t(12;16)(q13;p11)	Fusions	NGS, FISH, RT-PCR
	CREB/EWSR1	t(2;22)(q33;q12)	Fusion	NGS
	ATF1/EWSR1	t(12;22)(q13;q12)	Fusion	NGS
Synovial Sarcoma	*SS18, SS18L1*	t(X;18)(p11.2; q11)	Fusions	NGS, FISH
Extra-Renal Rhabdoid Tumor	*SMARCB1 (INI1)* and *SMARCA4 (BRG1)*	----	Variants, partial deletions	NGS
Epithelioid Sarcoma	*SMARCB1 (INI1)* and *SMARCA4 (BRG1)*	-----	Variants, partial deletions	NGS



Giemsa stain in a particularly over-stained area - a beautiful Artifact. Image courtesy: Ziad El-Zaatari, MD

CHAPTER 19: LABORATORY MANAGEMENT

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19. LABORATORY MANAGEMENT

REGULATORY BODIES & ACCREDITING AGENCIES

CLIA 88 - 42 CFR PART 405

- CLIA '88: Clinical Laboratory Improvement Amendment to the Clinical Laboratory Act of 1967
- Intended to improve quality, reduce errors
- Administered by Health and Human Services via CMS and FDA
- Requires certification for any laboratory performing tests for diagnosis, prevention, treatment, monitoring
- Certification obtained from CMS or accreditation programs with deemed status (CAP, JCAHO)
- Compliance with regulations required to receive payments

CLIA '88: CATEGORIZATION OF TEST COMPLEXITY

- **Waived:** Presents little risk if improperly performed
- **Moderate and High Complexity:** 7 Criteria
  - Knowledge required to perform test
  - Training required to perform test
  - Complexity of test preparation
  - Complexity of operational steps
  - Calibration, quality control and proficiency testing
  - Complexity of troubleshooting and maintenance
  - Level of judgement required to perform test
- **Provider performed microscopy**
  - When specimen is labile, and delay will impact accuracy
  - No controls available for monitoring test process
  - Limited to unstained microscopic evaluations

CLIA '88 CERTIFICATES

- **Waiver:** issued to sites performing only waived tests
- **Provider Performed Microscopy:** issued to sites performing test as part of patient examination
- **Compliance:** issued to sites that perform moderate or high complexity tests and surveyed by CMS or state health agency
- **Accreditation:** issued to sites that perform moderate or high complexity tests and surveyed by an organization with CMS deemed status

ELEMENTS OF CLIA '88 REGULATIONS

- **Inspections**
  - Routine inspections every 2 years
  - Performed by CMS, state, or agency with deemed status from CMS
  - Application (F116) includes specific tests and volume performed
- **Quality Control**
  - One set of standards for all non-waived testing
  - Adequate general laboratory infrastructure
  - Temperature and humidity monitoring
  - Reagents, controls, calibrators labeled and not outside expiration date
  - Written policies and procedures to include specimen requirements, preparation of reagents, calibration, QC and corrective action procedure, QA, result reporting, limitations of method, expected values, references
- **Quality Systems (program must encompass):**
  - QC and PT
  - Accuracy and timeliness of results
  - Specimen requirements/rejection criteria
  - Personnel qualifications, competency
  - Problem identification/remedial action
  - Result reporting and communication with clinicians
  - Calibration and method validation standards
- **Patient Test Management (standards for):**
  - Specimen: collection, labeling, preserving, transporting, and processing
  - Requests: only from authorized staff and include patient name, identification number, person requesting test, collection date, time, age, sex, relevant clinical data
  - Records: maintain at least 2 years (5 years for immunohematology, 10 years for anatomic pathology)
  - Reference Labs: must have appropriate CLIA certificate
- **Proficiency Testing**
  - Lab must enroll in approved PT program for each moderate/high complexity test on list of regulated analytes defined by CLIA
  - Successful PT defined as meeting target value >80% of time for each analyte in the challenge
  - Failure: Defined as unsatisfactory performance in 2 consecutive or 2 of 3 challenges
  - Lab may not report patient results for any analyte that it has failed and must develop remedial action plan
  - If no PT available, the lab must demonstrate proficiency by internally developed system

APPROVED CLIA ACCREDITATION ORGANIZATIONS

- American Association of Blood Banks (AABB)
- American Osteopathic Association (AOA)
- American Society of Histocompatibility and Immunogenetics (ASHI)
- College of American Pathologists (CAP)
- Commission on Office of Laboratory Accreditation (COLA)
- Joint Commission on Accreditation of Healthcare Organizations (JCAHO)
- States of Washington and New York have deemed status: meet or exceed CLIA requirements
- CLIA does not have specific waived test requirements, JCAHO and CAP do

COLLEGE OF AMERICAN PATHOLOGISTS (CAP)

- CAP Program for Lab Accreditation (LAP)
- Designed for hospital and independent labs, not for POLs or limited-service labs
- Peer review: utilizes lab professionals in actual practice

- **Focus:** systems essential to providing safe, high-quality care
- Inspector utilizes checklists
- Answer each question: Yes, No, Not Applicable
- Each question designated as:
    - **Phase 0:** informational only
    - **Phase I:** important aspects of lab operation; must be corrected
    - **Phase II:** significant impact on patient care or lab safety; must be corrected before accreditation is issued

JOINT COMMISSION ON ACCREDITATION OF HEALTHCARE ORGANIZATIONS (JCAHO)

- Inspects hospitals in addition to labs
- Professional surveyors
- No checklists: JCAHO standards leave some room for interpretation and for each organization to define its procedures and policies within regulations mandated by CLIA '88
- Looks for clear definition of lab policy and adherence to that policy
- Focus: performance improvement, outcomes, systems
- Preparation vs. continuous operation
- Priority focus process
- Elements of performance
- Tracer methodology
- Scoring: compliant or non-compliant
- Requirements for improvement

FOOD AND DRUG ADMINISTRATION (FDA)

- Licenses lab test systems prior to commercial use
- Classifies tests as required by CLIA
- Manages Safe Medical Device Act: requires report of adverse patient outcome due to medical devices
- Regulates interstate commerce of medical devices including reagents and instruments
- Licenses facilities that manufacture or transfuse blood components
- Transfuse only: must register
- Manufacture components: must have license

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA)

- Occupational Safety and Health Act (1970)
- Regulations require safe work environment
- May perform unannounced inspections based on reports from workers or identified even Exposure control plan
- 1991: Amendment to include exposure to blood borne pathogens
- Appropriate equipment and training
- Immunization programs
- Procedures for waste disposal
- Procedures for labeling containers of blood or other infectious material

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

- 1996 PL 104-191 passed in Congress; privacy regulations required by 1999
- 1999 Department of Health and Human Services proposed regulations
- 2002 Department of Health and Human Services issued final rule and guidance
- April 14, 2003 - Privacy Rule Compliance
- Goal: improve the efficiency and effectiveness of the healthcare system
- Portability of insurance: COBRA benefits
- Privacy-Use and disclosure of patient protected information
- Security-Protect patient information and systems used to store or process information
- Balance protection of individual rights with public health or safety needs of society
- Allows use of protected information for treatment, payment and operations
- Establishes "Minimum Necessary Disclosure"
- Prohibits certain uses of information, sale or barter of information, disclose information to non-healthcare affiliate, determine employment
- Establishes minimum privacy requirements
- Protect against unauthorized use and disclosure of protected health information
- Protect against adulteration of information
- Protect against destruction, loss, inaccessibility, or inability to use information

REIMBURSEMENT

METHODS OF REIMBURSEMENT

- Bundled with other patient services (DRGs)
- Fee schedule
- Fee for service
- Payment on account factor (PAF)
- Self-pay
- Free care

MEDICARE

- Federal program established in Title XVIII of Social Security Act, administered by the CMS, a division of DDHS
- Provides affordable care to elderly (over 65) and those meeting criteria for disability or end stage renal disease
- Law mandates:
    - Federal government will not dictate medical practice
    - Federal government will only pay for reasonable and necessary services to diagnose, treat, or monitor medical condition

19. LABORATORY MANAGEMENT

CENTER FOR MEDICARE AND MEDICAID SERVICES (CMS)

- Maintains Medicare program
- Establishes eligibility criteria for individuals
- Establishes services eligible for payment
- Establishes eligibility criteria for providers
- Administers agreements with states and intermediaries
- Manages finances of the program

MEDICARE COVERAGE FOR OUTPATIENT LABORATORY SERVICES

- Laboratory tests based on a fee schedule
- Physician professional fees based on Resource Based Value Scale (RBVS) using formula based on standard expense variables and local expense factors
- Balanced Budget Act 1997: Changed outpatient services to single payment based on Ambulatory Payment Class (APC) (same concept as DRG); physician and laboratory services excluded
- 345 APCs cover surgical procedures, ancillary services, medical visits, partial hospitalization

MEDICARE PAYMENT FOR OUTPATIENT LAB SERVICES

- **Based on:**
    - A. Regional fee schedule: 60% of prevailing charge = 75th percentile
    - B. CMS national cap: 76% of median fee schedule
- What you get: lesser of A or B or actual charge
- Result: hospitals attempt to maximize outpatient revenue and reduce inpatient utilization
- Exception: outpatient services provided within 72 hours of admission become part of DRG expense
- Billed using Common Procedure Terminology (CPT) code assigned by the AMA
- Most lab CPTs are based on specific analyte
- Automated Test Panels: analytes commonly performed on multichannel analyzers
- Two or more common tests rolled up into an automated panel code from 1-22 tests
    - Ex: Sodium, calcium, alkaline phosphatase = 3 test panel
- CPT defined specific organ system and disease panels
- Payment = lesser of panel or sum of individual tests

MEDICAL NECESSITY AND LOCAL MEDICAL REVIEW POLICIES

- Medicare only covers medically necessary services
    - Specifically: Medicare covers limited routine physical check-ups, including screening test
- 1996: medical necessity became a key element in reimbursement and compliance
- Fraud (intentional) and abuse (unintentional) claims settled especially for commercial labs
- LMRP: developed by carrier or intermediary
    - Restricts diagnoses for which test may be performed
    - Ex: tumor markers, thyroid function, cholesterol, etc.
    - Restricts how frequently a test can be performed

REQUIREMENTS FOR SUBMITTING A CLAIM

- Billing information for patient
- Date of service for test
- Name and address of testing location
- CLIA certificate number of testing location
- CPT for procedure
- Revenue code for procedure
- Documentation of medical necessity

MOST FREQUENT REASONS FOR MEDICARE DENIALS

- Test not covered
- Medical necessity rules not met
- Patient is not a Medicare beneficiary
- Lab is not a Medicare provider or CLIA-approved
- Insufficient documentation
- Medicare is the secondary payor

MEDICAL NECESSITY COMPLIANCE

- Physicians must:
    - Provide diagnosis or condition that justifies each test
    - Signs or symptoms may be used
    - Use the most specific ICD-10 code possible (ICD = International Classification of Disease)

BILLING MEDICARE PATIENT DIRECTLY

- Patient must be notified in advance that the test will likely be denied payment and sign "Advance Beneficiary Notice (ABN)
- Reasons for denial:
    - Carrier determines test is experimental
    - Test is ordered more frequently than allowed
    - Carrier determines test is not medically necessary
    - Carrier determines test was ordered as a screen

ADVANCED BENEFICIARY NOTICE (ABN) REQUIREMENTS

- Use standard form (CMS-131-G or CMS-131-L)
- State the reason for denial
- List the specific test(s) subject to denial
- Provide a reasonable estimate of charges
- Include the signature of beneficiary or witness

MEDICAID

- Federal funding and federal program, administered and managed by individual states
- Coverage for poor, medically indigent, and low-income families
- Covers inpatient, outpatient, home health, nursing home, some health screening
- Many states have programs for: pregnant women, children, disabled persons
- Matching federal funds for: prescription benefit, dental, hearing aid, etc.
- Each state defines eligibility criteria within federal guidelines
- CMS monitors state programs, payment models, level of coverage

19. LABORATORY MANAGEMENT

PRIVATE INSURANCE REIMBURSEMENT

- **Traditional Indemnity Plan**
  - Beneficiary or employer pays premium to insurance company
  - Patient selects provider (no restrictions)
  - Provider submits bill and is paid charges (or a percent of charges)
  - Patient may be responsible for charges not covered
- **Managed Care**
  - Restricts covered services by diagnosis
- **Capitated Plan**
  - Predetermined flat rate payment based on number of enrollees in plan
  - Provider assumes risk and cost that exceeds the monthly payment (e.g. $5 per member per month)
- **Four Typical HMO Models**
  - **Individual Practice Association (IPA):** physician group receives fixed payment from HMO to treat its patients
  - **Group Model:** physician group(s) contracts with HMO to provide services
  - **Staff Model:** physicians hired by HMO as employees
  - **Mixed Model:** features of various models

STARK LAW / SELF-REFERRAL LAW – BASIC RESTRICTIONS

- Physician may not refer a patient to an entity for a designated health service (DHS) covered by Medicare if the physician (or immediate family member) has a financial relationship with the entity
- Specific exceptions will allow the referral:
  - **Exception:** ancillary services provided in the office
- Service must be supervised by the physician or physician in the group
- Service must be provided in the same or centralized building
- Service must be billed by the physician or group and use their billing number
- Special requirements for billing company
- Practice must meet Stark definition
  - Exception: academic medical center
- Physician must be an employee of the AMC with a faculty appointment at the medical school
- Physician must provide a teaching service (clinical or academic) with compensation
- Compensation set in advance and at fair market value

MEDICARE ANTI-KICKBACK STATUTE / LAW (U.S.C. SECTION 1320A-7B(B))

- A lab may not discount lab testing, for non-Medicare patients, below the cost of testing
- Specific exceptions (safe harbors) may apply:
  - Space or equipment rental - payments to employers
  - Referral services - management contracts
  - Warranties - sales of practices
  - Discounts

LABORATORY FINANCIAL CONSIDERATIONS

BUDGET

- A planning tool that reflects projected revenues, expenses and (cash flow)
- Types of budgets: capital, operating, personnel, and allocation

OPERATING BUDGETS

- Ongoing expenses of operations considering all the costs of day-to-day operations, including:
  - Reagents and other consumables
  - Cost of reference lab tests
  - Costs of blood for the transfusion service
  - Professional fees
  - Depreciation, maintenance, and non-consumable equipment ("small ticket" items such as computer monitors)
- Includes:
  - Labor: salary, benefits, overtime, temporary or contract workers
  - Supplies: reagents, consumables
  - Leases: space, equipment
  - Equipment maintenance
  - Overhead

CAPITAL BUDGETS

- One-time expenses for "big ticket" items whose cost and return on investment may be mapped over more than 3 years
- Usually for purchase of equipment and renovations

PERSONNEL BUDGETS

- The projection of personnel needs, generally expressed in full time equivalents (FTEs)

ALLOCATION BUDGET

- The laboratory's allocated share of the hospital's fixed costs (e.g., electricity, administration, marketing)

PRINCIPLES OF OPERATING BUDGET

- Revenue – Expenses = Net Contribution or Profit (positive value)
- Revenue – Expenses = Deficit (negative value)
- Budget reports include current month and year-to-date (YTD)

REVENUE VS. INCOME

- Revenue (Gross Revenue) - total funds generated by the sales of a good or service before expenses are paid
  - Charge x Volume
  - Payor Rate x Volume

- Income (Net Revenue or Profit) = total revenue (gross revenue) – fixed cost – variable costs
  - Funds remaining after all expenses have been paid

TYPES OF COST

- **Direct:** related directly to production of a product or are incurred directly from the performance of the test
  - Examples: labor, reagent, supplies, quality controls, instrument purchase, technologist wages
- **Indirect:** not related to product produced but is necessary to create environment for production
  - Examples: supervisor labor, building maintenance, rent for laboratory space, custodial services, depreciation
- **Overhead:** costs that do not directly contribute to revenue
  - Examples: administration (local and global), utilities
- **Fixed:** does not vary over time or volume and are largely unaffected by the number of tests performed
  - Examples: rent, license, overhead, management, service contracts, marketing, supervisor wages
- **Variable:** varies over time or parallels volume; are affected by the number of tests performed
  - Examples: reagents, supplies, technologist labor, overtime
- **Semi-variable (or step variable):** varies with volume, but not in direct proportion to volume
  - Examples: Labor – lab may absorb some increased volume without added labor but at some point, a new technologist will be needed

GOALS OF COST ACCOUNTING (CALCULATING COST/TEST)

- Track revenues and expenses
- Measure operating performance
- Measure financial performance
- Budget resources
- Aid in decision making

COST ACCOUNTING - TWO METHODS TO CALCULATE COST/TEST

- Job order costing: calculate costs for a single test
  - Accurate but demanding
  - Helpful if product is heterogeneous
- Process costing: calculate total costs and then divide by units produced
  - Less accurate
  - Most useful if product is homogeneous

CALCULATION OF THE COST PER TEST

- Define units of analysis (e.g., all tests or single analyte or procedure)
- Identify direct costs: salary, supply, reagents
- Identify indirect cost: utility, space (usually a fixed institutional rate)
- Distribute costs to units of analysis - Total Costs/Units of Analysis

BREAK-EVEN POINT ANALYSIS

- Purpose of doing a break-even-point analysis (BEP) is to determine the point at which the cost for the volume of tests equals the revenue generated. This volume of tests is called the break-even point.
- BEP can be calculated for individual tests, specific testing instruments, a cost center, or the entire laboratory.
- The idea is that if the BEP is not reached in a fiscal year or well along in the fiscal year, operation adjustments are probably in order
- The sooner the BEP is reached, the more financially viable a test, instrument, or cost center becomes.
- BEP analysis requires that testing expenses be divided into fixed and variable costs. The net income contribution in this equation is set at zero because when costs equal revenues, this will be the net income contribution

$$BEP = \frac{F + C}{r - V}$$

r = revenue per reportable test
V = variable cost per reportable test
F = total fixed costs
C = net income contribution (set at zero)

VARIANCE ANALYSIS

- Difference between actual performance and budget performance
- Look at dollar variance and percent variance from budget
- Verify budget numbers
- Verify expenses and supporting details
- Adjust budget or expenses
- Possible causes of a variance
  - Errors in budget assumptions
  - Billing mistakes by vendors
  - Staffing problems (over- or understaffed)
  - Volume increases or decreases
  - Bulk purchase – expensed in one month
  - Service contract - annual expense realized in current month

THE CAPITAL BUDGET

- Hospitals have a fixed annual capital budget dollar amount that is set by Trustees
- All departments compete for the dollars
- Supplemented by emergency funds for unexpected purchases (e.g., an instrument breaks and must be replaced)
- Capital budget is separate from operating budget
- Capital budget in the laboratory includes:
  - Instrument purchase
  - Lab information system purchase
  - Personal computers
  - Renovations, furniture
- New equipment must be justified based on net present value, payback period, or other

19. LABORATORY MANAGEMENT

CAPITAL JUSTIFICATION: NET PRESENT VALUE ANALYSIS

- Analyze cash outlays
- Analyze cash recovery (revenue, labor savings)
- Discount for lost interest if cash was held in alternative investment (time value of money)
- Usually depreciation is straight line (equal amount over each year)

CAPITAL JUSTIFICATION: PAYBACK PERIOD

- Time to repay original capital
- Alternative use of capital (time value of money not considered)
  - ➢ Example: Purchase cost $100,000
    Instrument generates $20,000 per year
    Payback: 5 years (100÷20=5)

CAPITAL ACQUISITION

- **Purchase**
  - ➢ **Advantages**: usually discounted off list price (typical discount 20-65%); reagents are less than a lease and total cost over time is usually less; can be depreciated
  - ➢ **Disadvantages**: you own it; locks you into a technology; capital may not be available, or you may need to forego other purchases
- **Lease**
  - ➢ **Advantages**: no capital required; time (no need to wait for annual capital budget cycle); can modernize or change technology if needed
  - ➢ **Disadvantages**: reagents more expensive per test; breaking lease may force you to buy lease out; total cost usually higher than purchase
- **Reagent Rental**
  - ➢ You pay a fixed amount for reagents on per test basis
  - ➢ The equipment cost and maintenance are built into the reagent agreement
  - ➢ **Advantages**: time (easy to set up); no capital; easy to change technology
  - ➢ **Disadvantages**: reagent and total cost highest of all three models

PERFORMANCE IMPROVEMENT AND QUALITY METRICS / IMPROVEMENT

WHY DO PERFORMANCE IMPROVEMENT?

- Institute of Medicine (IOM) Study: 44,000-98,000 deaths per year in the U.S. hospitals due to medical error
- Patients and providers expect perfect service and error-free information
- Employees want an opportunity to work in an organization that provides the best possible care
- Quality is cost effective
- **IOM characteristics of quality healthcare:**
  - ➢ Safe
  - ➢ Effective
  - ➢ Patient-centered
  - ➢ Timely
  - ➢ Efficient
  - ➢ Equitable

QUALITY SYSTEM HIERARCHY (IN INCREASING SCOPE)

- Quality Control
- Quality Assurance
- Quality Systems
- Quality Management
- Total Quality Management

QUALITY CONTROL

- Intent: produce accurate, precise, and timely information

QUALITY ASSURANCE

- System or process interventions aimed at fulfilling quality expectations or requirements
- Identifying and removing barriers or variation within the system or process and monitoring the effect
- Intent: to prevent error and to improve quality
- Monitors outcome, appropriateness, cost-effectiveness, service
- Looks at the overall process including preanalytic, analytic, and postanalytic phases and includes inter-departmental activities

Total Quality Management (TQM)

- Philosophy that seeks to integrate all organizational functions (production, finance, information systems, etc.) to fulfill customer needs
  - ➢ Customer-focused approach with long-term value
  - ➢ Quality is a part of all management activities
  - ➢ Continuous improvement

Quality control (QC) and Walter Shewhart

- Focuses on product in order to detect system errors
- **Shewhart promulgated the concept of acceptable variation**
- Variability is inherent in all processes
  - ➢ Limits of acceptability should be statistically defined
  - ➢ Processes should not be adjusted when products fall consistently within them
- When outside defined limits, the process should be inspected for "assignable causes"
- To define limits, Shewhart plotted data on a control 4 chart, a graph with lines demarcating the mean and several SD
- Levey & Jennings utilized Shewhart control charts in the clinical laboratory ("Levey-Jennings" charts)
- The process became known as statistical quality control (SQC)
- **6 Sigma** is an extension of the SQC concept, the name referring to 6 SD from the mean
  - ➢ The premise in 6 Sigma is that a process design in which limits of acceptability are 6 SD from the mean has a very low likelihood of failure; specifically, 3.4 defects per million (2 sigma produces 308,000 per million)

19. LABORATORY MANAGEMENT

STATISTICAL QUALITY CONTROL / TRADITIONAL QC

- Refers to parallel testing of known samples to ensure that the **test system is working properly** and that results obtained from patient samples are **reliable**
- Specimens used for QC are most often samples provided by an outside vendor
- For each type of quantitative test, there are usually 2 or 3 controls used:
  - A "low" QC reagent, a "high" QC reagent, and sometimes a "midrange" QC reagent
  - Often referred to as level 1, level 2, and level 3 controls
- When a new control lot is received, it is tested several times (usually 20 times)
  - The results from these tests are used to calculate a mean and standard deviation (SD)
  - Based on these, a Levey-Jennings (Shewhart) chart is created

FREQUENCY OF CONTROL SAMPLE ASSAY

- Usually once per level per run but may be done only once per day, depending on the type of test and its frequency
- At minimum, CLIA requires 2 levels of QC every 24 hours (if testing is performed during the 24-hour period) or as frequently as recommended by the manufacturer, whichever is more frequent, unless an alternative plan is implemented
- Application of control sample test result:
  - The result obtained is plotted on the Levey-Jennings chart
  - If the control sample result falls within 2 SD of the mean, the run is considered "in control," and the results of patient samples can be reported
  - If the result falls outside 2 SD of the mean, Levey-Jennings chart is interpreted in terms of Westgard rules and based on this, the run is determined to be "in control" or "out of control."
  - The results of "out of control" runs should not generally be reported

WESTGARD RULES

- **2 SD rule** - an indication for further review of QC data
- It is expected that about 5% of QC results will fall outside 2 SD

Select Westgard Rules

Rule	Definition	Purpose
1:3s	1 value within ±3SD from the mean	Detect imprecisions
2:2s	2 consecutive values >2SD on same side of mean	Detects imprecision & bias
R:4s	2 values within the same run >4SD on same side of mean	Detects random error
4:1s	4 consecutive values >1SD on same side of mean	Detects systematic bias
10:mean	10 consecutive values on same side of mean	Detects systematic bias

- The 2:2s, 4:1s and 10:mean rules are sensitive to system errors, which could result in shifts or drifts (trend)
  - **Drift**: gradual movement away from the mean; causes include slow deterioration in a light source, corrosion of electrodes, accumulation of debris within tubing, or reagent deterioration
  - **Shift:** rapid and sustained move away from the mean; causes include altered temperature or humidity, lot changes, instrument maintenance, or failure in any number of system components
- The R:4s and 1:3s rules are most sensitive to random error, which may be caused by bubbles, underfilled tubes, technologist error, and auto pipetting errors

WHEN AN "OUT OF CONTROL" RUN IS DETECTED

- Evaluate the test system including reagents and instrument
- After doing this, it is acceptable to repeat QC testing on a new aliquot of the QC reagent
- If this is substantially within acceptable limits, then it is possible that QC reagent handling or deterioration was the culprit, and patient results from the run may be reported
- If repeat testing is not within acceptable limits, a thorough check of the instrument and reagents must be undertaken
  - Suspected problems are corrected, and QC reagents are retested to ensure resolution
  - If this corrects the problem, patient samples must be repeated before reporting
- If QC results are still not acceptable, then the next step is to repeat calibration and repeat testing on the QC reagents, then repeat patient testing if appropriate
- Persistence of an “out of control” assay may require formal instrument maintenance
  - Testing should be shifted to the backup instrument or sent to another laboratory in the meantime

QC SPECIMENS

- May demonstrate matrix effect
- May require reconstitution or dilution, which can be a source of error
- May undergo deterioration during storage
- May be commutable or non-commutable
  - **Commutable QC reagents:** biologically similar to patient samples whose results are directly comparable to them
  - **Non-commutable reagents:** have altered constituents such as the matrix

ALTERNATIVES TO TRADITIONAL QC

- Beginning in 2004, CMS began to permit individualized QC plans (IQCP) as an alternative to traditional QC
- As of 2016, equivalent QC (EQC) was discontinued as an alternative to traditional QC
- IQCP – QC plan customized for a test based on risk management principles

- Risk analysis must be performed upon the test prior to implementation
- Risk analysis may justify a QC plan that is less stringent than traditional QC
- Labs are required to perform 2 levels of liquid QC per day (or more if recommended by manufacturer) for all nonwaived tests unless an IQCP analysis has been conducted that permits an alternate plan (while still satisfying at a minimum the manufacturer's recommendation)
- The requirements for IQCP include ongoing risk assess and effectiveness monitoring

PERFORMANCE IMPROVEMENT

- JCAHO Standard
- An organization's performance of important functions significantly affects the quality and value of its services
- Ensure that the organization designs processes well
- Systematically monitors and analyzes
- Improves its performance to improve patient outcomes

JCAHO MODEL FOR PERFORMANCE IMPROVEMENT

- Assign responsibility
- Delineate scope of services
- Identify important aspects of care
- Identify indicators (e.g., STAT turnaround time, computer downtime, number of needlestick injuries, etc.)
- Establish thresholds for indicators
- Collect and organize data
- Evaluate issues when thresholds are exceeded
- Take action to correct problems
- Reassess effectiveness and document performance
- Communicate organization-wide

JCAHO: SENTINEL EVENTS

- **Definition**: "unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof"
- Examples: unanticipated death, major permanent loss of function not related to initial condition
    - ➢ Suicide
    - ➢ Infant abduction or incorrect discharge
    - ➢ Hemolytic transfusion reaction
    - ➢ Surgery on wrong patient or location
    - ➢ Organization should use event to analyze causes and make changes

CLIA - QUALITY SYSTEMS

- Comprehensive program to meet quality objectives
    - ➢ Accurate, reliable, timely
- Facilitates error identification, reduction, or prevention
- Patient test management, quality control, and quality assurance combined into:
    - ➢ Facility administration
    - ➢ Quality system

ROOT CAUSE ANALYSIS (RCA)

- Identifies variables that cause changes in performance variables
- Focus on systems, workflows, processes
- Looks for special causes and common causes
- Identifies opportunities to improve process or system
- Results in action plan with implementation strategies

Failure Mode and Effect Analysis (FMEA)

- Proactive process to improve patient safety
- Method:
    - ➢ Define topic
    - ➢ Map out process flow
    - ➢ Identify potential failure points
    - ➢ Rate failure points for probability and severity
    - ➢ Identify failure point(s) to be corrected
    - ➢ Develop improvement strategy and measurement tool

NCIS MODEL OF QUALITY SYSTEMS

- **Organization:** management planning for quality
    - ➢ Programmatic issues, policies and procedures, regulatory compliance
- **Personnel:** job qualifications, training, competency assessment, performance assessment
- **Equipment:** selection, validation, calibration, maintenance
- **Purchasing and inventory:** reagents, supplies, vendor issues
- **Process control:** measures performance against standards including QC and QA
- **Documents and records:** document control plan
- **Occurrence management:** incidents and errors
- **Internal assessment:** systematic process for monitoring quality metrics
- **Process improvement:** the desired outcome of the quality system
    - ➢ Often involves Pareto analysis, Fishbone (Ishikawa) diagrams
    - ➢ Pareto= error frequency histogram
    - ➢ Fishbone= process diagram with relation between steps
- **Service and satisfaction:** Measure quality of services in terms of customer needs and expectations

TOOL: PLAN – DO – CHECK – ACT (PDCA) CYCLE

- **Plan:** identify opportunities, measure current performance, develop improvement plan with measurable goals
- **Do:** define solutions and conduct pilots
- **Check:** verify outcomes of pilots with desired outcome
- **Act:** standardize & implement solutions with ongoing monitors

TOOL: SIX SIGMA (DMAIC)

- Define the problem
- Measure the baseline
- Analyze the root causes
- Improve by designing solutions
- Control by ongoing measurements

19. LABORATORY MANAGEMENT

COMPONENTS OF A QUALITY ASSURANCE PROGRAM

- Management of patents, specimens, and tests
- Quality control and instrument calibration data
- Establishment of reference ranges
- Proficiency testing
- Validation of test results
- Personnel
- Documentation of communication between laboratory and physicians
- Investigation of problems and patient/physician complaints
- Communication of quality assurance activities with personnel
- Written documentation of quality assurance activities

TYPES OF MONITORS FOR USE IN QUALITY ASSURANCE

- **Metrics and Statistics** (e.g., test volumes, turnaround times)
- **Appropriateness:** monitors clinical decisions and policies (e.g., utilization monitors, selection of appropriate tests)
- **Incidents/occurrences:** identifies adverse consequences (e.g., complications, misdiagnoses, adverse reactions)

SOURCES FOR PERFORMANCE IMPROVEMENT OPPORTUNITIES

- Proficiency, quality control problems
- Competency assessment
- Patient complaint
- Provider complaint
- Employee complaint
- Incident reports
- Sentinel Events
- Staff and customer surveys
- JCAHO preparation and survey
- Inspections

CRITERIA TO SELECT PERFORMANCE IMPROVEMENT PROJECTS

- High risk, high volume, problem-prone
- Potential Impact - size of population; clinical; financial
- Support mission and strategic plan
- Resources – people (time, skills), financial, space
- Timeline
- Balance Goals

PROFFICIENCY TESTING

PROFICIENCY TESTING (PT)

- One of the **central safeguards of laboratory quality** under CLIA and its regulations & only **required external performance** indicator
- Laboratories must demonstrate successful PT performance to remain in good standing
- Successful performance is defined based on satisfactory performance on individual PT events (occur 3x/year)
- Each event has five challenges per analyte per event and laboratories must get at least four challenges correct (80%), or the event will be considered as unsatisfactory
- If a laboratory has two unsatisfactory events out of three consecutive events, it will be cited with a deficiency
- If the laboratory does not submit its result on time or fails to submit them at all, then a laboratory will usually obtain a score of 0%
- Laboratories must be sure they are aware of all the required PT analytes listed in the regulations and enroll in a PT program for those analytes if they perform patient testing for them
- PT samples should be tested in the same manner as the patient specimens (i.e., integrating the sample into the normal patient workload) without assigning to the "best techs" for analysis
- It is important to avoid splitting a PT specimen for testing with any other laboratory that has a different CLIA number, whether internal or external to your laboratory system
- Laboratory staff may not discuss PT results with laboratories in their system that have a different CLIA number or with external laboratory staff, as may be possible when they work two jobs

SPECIAL CASES

- **Microbiology**
    - ➢ Microbiology does not have specific PT analytes as indicated for other laboratory specialties
    - ➢ Instead, CLIA requires laboratories to enroll in PT for each subspecialty of microbiology (bacteriology, mycobacteriology, mycology, parasitology, and virology) for which they perform testing
- **Gynecologic cytology**
    - ➢ Cytology differs from other specialties in that individual cytotechnologists and cytopathologists who screen gynecologic cytology specimens (Pap tests) must participate in on-site PT at least once per year
    - ➢ The passing score is 90% on the annual ten-slide test set (if someone doesn't pass, they must be retested)
    - ➢ If the individual does not achieve a passing score on the second test, he or she must receive remediation, and gynecologic slides he or she examines must be rescreened before the individual is again retested using a 20-slide test set
    - ➢ If no passing score is achieved on the third test, he or she must cease examining gynecologic slides and receive 35 hours of continuing education in diagnostic cytopathology that focuses on the examination of gynecologic slides
    - ➢ The individual may not resume examining gynecologic slides until he or she achieves a passing score of 90%.
- **Immunohematology (blood banking)**
    - ➢ For each PT event, criteria for acceptable performance for ABO group, Rh typing, and compatibility testing is 100% accuracy

19. LABORATORY MANAGEMENT

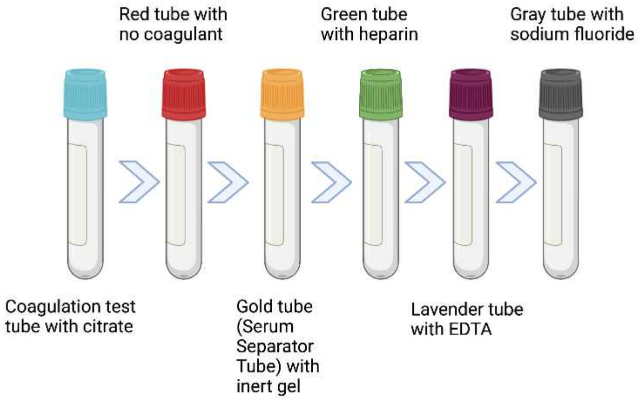
VARIABLES & ERROR IN LABORATORY MEDICINE

PREANALYTICAL VARIABLES

- **Account for 65% of errors**
- Occurs as soon as specimen is acquired
- Includes specimen acquisition, transport, and processing
- **Patient identification** is one of the common errors
  - CAP requires two patient identifiers on the sample
  - Specimen should be labeled in the presence of the patient
- **Delta checks** may detect patient identification errors
  - Compare current result values with previous result values and identify samples that have exceeded predefined acceptable limits for variation
  - Laboratories determine which assay will have delta checks
- **Examples of common preanalytical errors:**
  - Misinterpreting the test ordered
  - Patient identification
  - Incorrect sample collection
  - Patient not well prepared before sample collection
  - Wrong collection container
  - Labeling requisition form wrong
  - Transporting sample under wrong conditions

PATIENT VARIABLES

- **Age**
  - Neonates have a relatively higher mononuclear cells than adults
  - Adolescents have higher alkaline phosphatase than adults
  - Elderly patients have decreased creatinine clearance, glucose tolerance, increased lipids
- **Gender**
  - Males have increased creatine kinase 9CK) and lower LDL as compared to females
- **Diet**
  - Glucose and triglycerides can significantly increase after meals with high carbs and fat
  - Gastrin and insulin are elevated following a meal
  - Bilirubin is decreased following a meal
  - Caffeine and alcohol are common drinks that can affect analytes measurement
- **Exercise**
  - Lowers blood glucose levels and increases potassium, urea, creatinine, creatine kinase, lactate dehydrogenase (LDH), aspartate transferase (AST), alkaline phosphatases, bilirubin, uric acid, and white blood cell count
  - Exercise increases HDL levels
- **Posture**
  - A change from lying to standing can increase serum concentration of proteins or protein bound constituents
  - Mechanism: during standing there is increase hydrostatic pressure and protein free fluid moves out of the circulation → relative increase in proteins, blood cells and substances largely bound to proteins
- **Time of collection**
  - Some analytes are affected by time of the day
  - Cortisol levels are high in the morning
  - Serum iron level increases and serum potassium level decreases from morning to afternoon
- **Blood draw, storage, and transport conditions**
  - It is important to collect blood in a test tube in a particular order
  - The first should be for blood cultures
  - Some tests are done on anticoagulated whole blood (CBC), some on serum (serum protein electrophoresis) and some performed on plasma (coagulation tests)
  - Ideally test should be performed within 1-2 hours, but this is not always feasible
  - Sample should be stabilized if anticipating delay
  - Collection in the right tube is needed to maintain proper storage
  - Blood undergoes metabolism and slowly undergoes lysis → release of potassium from the cells
  - Sample for ammonia testing should be transported on the ice.


Red tube with no coagulant
Green tube with heparin
Gray tube with sodium fluoride
Coagulation test tube with citrate
Gold tube (Serum Separator Tube) with inert gel
Lavender tube with EDTA

ANALYTICAL VARIABLES

- **Account for 15% of errors**
- Analytical variables occur during actual testing of the specimen
- Performance of tests in the laboratory is rigorously controlled, with quality control procedures in place designed to reduce errors in the analytic phase of testing
- **Examples include:**
  - Failure in quality control
  - Result reported when control results out of range
  - Error in proficiency testing
  - Wrong method performed for the test
  - Reagents stored inappropriately

  - Expired reagents
  - Wrong test performed
  - Sample mix up in the lab
  - Instrument maintenance not performed
  - Diluting and pipetting errors

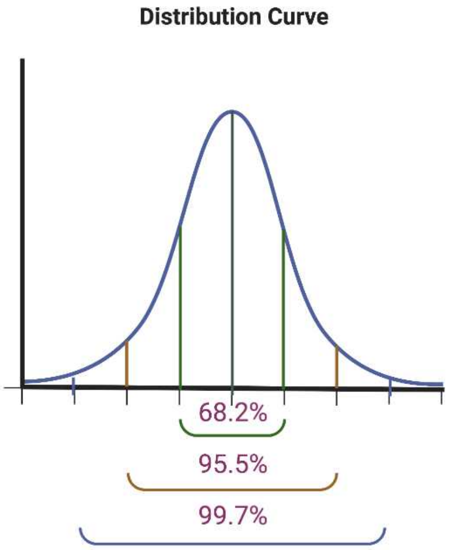
POSTANALYTICAL VARIABLES

- **Account for 20% of errors**
- Consists of steps after the test have been carried out
- Manually or automatically entering the results in the report forms
- **Immediately inform requesting clinician about critical results** (life threatening results)
  - Written procedure for critical values
  - Laboratory should have a list of critical values
  - Who is responsible to report and who is authorized to accept the results
  - What is the length of time that is allowed to report a critical value
- Errors in interpretation of the report

STATISTICS

LABORATORY STATISTICAL CONSIDERATIONS

- **Measures of central tendency and Gaussian distribution**
  - **Mean** is calculated by adding all the data values together, then dividing by the total number of values
  - **Median** is calculated by listing the data values in ascending order, then finding the middle value in the list
  - **Mode** is calculated by counting how many times each value occurs and the value with the highest frequency is the mode
- Gaussian curve shows data symmetrically distributed around the center with more values closer to the mean
  - In ideal gaussian curve: mean = median = mode
  - In positively or right skewed distribution, the tail on the right side of the distribution is longer (mean > median > mode)
  - In negatively or left skewed distribution, the tail on the left side of the distribution is longer (mode > median > mean)
  - 68.2% of population falls within ±1SD
  - 95.5% of population falls within ±2SD
  - 99.7% of population falls within ±3SD



CLINICAL SENSITIVITY AND SPECIFICITY

- **Clinical sensitivity:** ability of the test to identify diseased patients who have the condition
  - Sensitivity = (true positive) / (true positive + false negative)
- **Clinical specificity:** Is the ability of the test to reject healthy patients who do not have the condition
  - Specificity = (true negative) / (true negative + false positive)
- **Clinical sensitivity** and **specificity** are **not affected by the prevalence of the disease**

PREDICTIVE VALUE

- **Positive predictive value (PPV):** probability that a positive test result is true positive
  - PPV = (true positive) / (true positive + false positive)
- **Negative predictive value (NPV):** probability that a negative test result is true negative
  - NPV = (true negative) / (true negative + false negative)
- **PPV** and **NPV** are affected by the disease prevalence
  - If the disease prevalence is high, PPV is increased and NPV is decreased

RELATIVE RISK (RR)

- Estimate of strength of the association between exposures and outcomes
- Measures the risk of disease among the exposed to the risk among unexposed
- RR = incidence rate in exposed / incidence rate in the unexposed

	Disease present	Disease absent
Positive test	True Positive	False Positive
Negative test	False Negative	True Negative

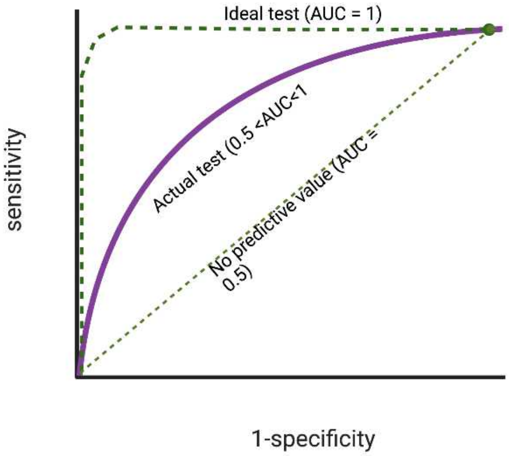
19. LABORATORY MANAGEMENT

RELIABILITY: ANALYTICAL ACCURACY AND PRECISION

- **Analytical accuracy:** the closeness of the value measured and a true value
  - ➢ It is the extent to which test result approximates the true value
  - ➢ The absence of systematic error in a test
  - ➢ It is reflected in the correlation coefficient of bias plots and is controlled through regular calibration
  - ➢ Analytical accuracy should be differentiated from diagnostic accuracy or clinical accuracy
- **Diagnostic accuracy:** the ability of a test to distinguish patient groups
  - ➢ Receiver operating characteristic curve and the dot diagram used to illustrate diagnostic accuracy
- **Precision:** reproducibility of the test
  - ➢ Controlled through regular testing of QC reagents
  - ➢ Imprecision is expressed in terms of coefficient of variation (CV = standard deviation / mean x 100)

RECEIVER OPERATING CHARACTERISTICS CURVE (ROC)

- The ability of diagnostic test to distinguish between two groups
- Higher area under the curve (AUC) → better performing test
- A test with no ability to distinguish will have AUC = 0.5, which is a diagonal line from the from the lower left corner
- An **ideal test has AUC = 1**



REFERENCE INTERVAL

- Reference interval is **required** in every test result
- The laboratory may use the manufacturer's reference range, if it is appropriate for the patient population
- Laboratory must verify manufacturer's reference range if they are using it and document how it was established
- The Clinical and Laboratory Standards Institute (CLSI) recommends testing **at least 20 healthy individuals and at least 18 should fall withing the established range (80%)**
- If reference range provided by laboratory is not appropriate, laboratory may use published reference ranges
- If new instrument or method is being implemented, laboratory may use its own previously established reference interval
- **Establishing reference intervals:**
  - ➢ Use a reference population of healthy individuals demographically comparable to the patient population
  - ➢ **Minimum of** 120 **healthy reference subjects** per partition, as recommended by CLSI
- By tradition, **reference interval includes 95% of the values** (usually the central 95%)
- For some analytes with biologic variation, population-based reference intervals will not be applicable
- Some analytes have no normal lower limit (e.g., prostate specific antigen, PSA)

THE RETENTION & USE OF HUMAN BIOLOGICAL MATERIAL

	Surgical Pathology	Hospital Autopsy
Wet Tissue	4 weeks after final report	3 months after final report
Frozen Tissue (e.g., renal bx)	Up to 20 years	
Paraffin Blocks*	20 years	10 years
Slides	20 years	10 years
Surgical Consultation	Indefinitely	
Paper Requisition	2 years	
Autopsy Records		Indefinitely

	Cytology
Slides (negative/unsat)	5 years
Slides (suspicious/positive)	20 years
FNA Slides	20 years
Consultation/Requisition	Indefinitely
Male fertility Slides	1 year
Paper Requisitions	2 years
Paraffin Blocks	20 years

*For special pediatric cases (i.e., Children's Hospitals), 50 years is the recommended minimum retention period for paraffin blocks

**Retention time for forensic autopsy: wet stock tissue (1 year), body fluid/tissue for tox (1 year), slides/paraffin blocks/reports (indefinitely), photos/log/DNA evidence (indefinitely)

Note: Electron microscopy material (blocks, slides/grids/photos) should be retained for 20 years